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Vol. 6 September 1959 No. 3

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Anthony C. Allison

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RECENT DEVELOPMENTS IN THE STUDY OF INHERITED ANEMIAS

ANTHONY C. ALLISON*
National Institute for Medical Research
London

THE STUDY OF INHERITED ANEMIAS received great impetus from the demonstration of Pauling, Itano, Singer and Wells (1949) of the presence of an abnormal hemoglobin in sickle-cell disease. In the succeeding decade research in this field has expanded enormously and produced results of considerable general interest. The rate of progress still shows no sign of declining, and it is to be hoped that the next ten years will prove as fertile as the last.

The developments have followed three main directions. Widespread application of filter paper electrophoresis has led to the recognition of more than thirty varieties of human adult hemoglobin and three varieties of human fetal hemoglobin. The overall distribution of the hemoglobin types in various human populations has been determined. This may be termed the classificatory phase of development of the subject—analogous to the phase of systematic description of flora and fauna in a new continent. Inevitably, there has been terminological confusion, and in their eagerness to describe new hemoglobin types some workers have relied on inadequate criteria for characterization, as Beaven and Gratzer (1959) have emphasized. On the other hand, some hemoglobin types thought to be the same have been shown to differ, e.g. the three varieties of D mentioned below. Powerful techniques for establishing identity or non-identity are now available, in particular peptide analysis, and in a few years many of the mutant forms will be chemically defined.

This represents the second major development in the field. The effect of several mutations has been identified as the replacement of one amino acid residue by another in half-molecules of hemoglobin. Moreover, it has become evident that the two unlike polypeptide chains of the hemoglobin molecule are synthesized under independent genetic

*Dr. Allison is Secretary of the Human Genetics Committee of the Medical Research Council.

control. The results have illuminated the genetic control of protein synthesis, which is a key problem in biology.

The third line of development has been concerned with the population genetics of the abnormal hemoglobins. It has been established that the high frequencies of the sickle-cell gene in many populations are due to a balance of powerful selective forces, some tending to increase and others to decrease the frequency of the gene. And it has been shown that as a rule any two abnormal hemoglobin types tend to be mutually exclusive in populations. These represent the best-understood examples of polymorphism and natural selection in man.

Another series of investigations of inherited anemias has also yielded results of general interest. These have been on the sex-linked trait for deficiency of the erythrocyte enzyme glucose-6-phosphate dehydrogenase. The trait is responsible for susceptibility to hemolysis on exposure to primaquine and other drugs and to fava beans. The high frequencies of this trait in many populations makes it a true polymorphism — one of the most remarkable sex-linked polymorphisms in any species.

Results of recent investigations of other inherited serum-protein differences —in particular, transferrin and haptoglobin types—show them to be analogous in some ways to the hemoglobin types, although there are certain interesting differences. These topics have been selected for discussion in this paper. No attempt has been made to cover the field comprehensively. General reviews are available on inherited hemolytic anemias (Dacie, 1954; Wintrobe, 1956), human hemoglobins (Itano, 1957; Beaven and Gratzer, 1959), primaquine sensitivity (Beutler, 1959) and haptoglobins (Allison, 1959a).

MUTATION AND HEMOGLOBIN TYPES

The genetic control of protein synthesis is an important problem in biology. This is so because protein enzymes appear to be responsible for the synthesis of all other bodily constituents, including complex polysaccharides and lipids, ribonucleic acid (RNA—Ochoa and Heppel, 1957) and deoxyribonucleic acid (DNA—Kornberg, 1957). By contrast, proteins cannot synthesize other proteins; evidence is accumulating that proteins are synthesized by microsomal particles and soluble cellular components containing RNA (see Crick, 1957; Work, 1959). This appears to be true also of hemoglobin (Schweet, Lamfrom and Allen, 1958). It follows that to exert their effects on the metabolism of cells genes have to act through proteins. Many workers believe that the sequence of bases along a span of chromosomal DNA determines uniquely the sequence of amino acids in the polypeptide chain of a protein (see Crick, 1957). This presumably takes place through the agency of a specific RNA-containing intermediate. A mutation or change in the base-sequence of a particular length of DNA would be expected to change the sequence of amino acids in the corresponding polypeptide chain.

Using the technique of peptide analysis developed by Sanger, Ingram (1957) and Hunt and Ingram (1958) have shown that precisely this occurs. The only detectable difference in hemoglobins S and C from A lies in the substitution of a valine and a lysine residue, respectively, for glutamic acid in each half-molecule. The differences in charge produced by these substitutions are sufficient to account for the overall differences in electrophoretic mobility of the

hemoglobin types. This small substitution has dramatic consequences: the change in charge allows the sickle-cell hemoglobin molecules to aggregate when deoxygenated and so brings about the sickling of erythrocytes, hemolysis and vascular obstruction characteristic of sickle-cell disease. Since it is likely that the sickle-cell and hemoglobin C genes have arisen as mutations from the normal allele, the effect of mutations can be defined as the replacement of one amino-acid by another in the gene products. On any coding hypothesis this is unlikely to involve change of more than a few base pairs of the DNA double helix; and it could be due to alteration of a single base pair. Benzer (1957) has defined a "muton" as the smallest genetic element that, when altered, can give rise to a mutant form of organism, and a "recon" as the smallest unit in the unidimensional array of genetic units that is interchangeable, but not divisible, by genetic recombination. His estimate of recon size, based on recombination studies in bacteriophage, is about 5 nucleotide pairs. Rosenberg, Sirotnak and Cavalieri (1959) have presented evidence that DNA fragments of the same order of size can bring about transformation in pneumococci. The evidence just quoted suggests that a muton is no bigger.

Benzer, Ingram and Lehmann (1959) reported the results of peptide analyses of three samples of an abnormal hemoglobin that were all thought to be D because they showed an electrophoretic mobility similar to that of S but had solubilities within normal limits. The three hemoglobins were found to be different from one another and from normal adult hemoglobin (HbA). This result raises the question whether other hemoglobins characterized by electrophoresis are the same. In fact, many abnormal forms of hemoglobin may not differ from HbA electrophoretically. In general it is clear that numerous mutant form of hemoglobin exist, some being physiologically normal and others defective, e.g. sickle-cell hemoglobin and the varieties of hemoglobin M that undergo spontaneous oxidation in methemoglobin (see Gerald and George, 1959).

Other developments have been reported by Ingram (1959). In hemoglobin E once again a glutamic acid residue of A is replaced by lysine, involving a change of two units of electric charge, in each half-molecule. However, this mutation is in a different peptide from the S and C mutations, and hence affects a different part of the molecule. The Dβ mutation affects the same peptide as is altered in E, but not necessarily the same amino acid. The Dα and I mutations both involve another peptide.

Peptides and proteins from different species often differ by single amino-acid substitutions (see Allison, 1959b), and again it is reasonable to suppose that each of these arose by single mutational steps. It seems clear that mutations do not affect all parts of the hemoglobin molecule with equal frequency but are particularly common at certain sites. The same is true of other proteins. Thus, the only differences in insulins from different species appear to lie in the 8·9·10 sequence of residues within the intra-chain disulphide bridge of the A chain (Harris, Sanger and Naughton, 1956; Ishihara, Saito, Ito and Fajino, 1958). The inference is that some parts of the DNA chain are inherently more unstable than others. Benzer and Freese (1958) have produced evidence that this is true of the bacteriophage chromosome both spontaneously and in the presence of a mutagen.

INDEPENDENT GENETIC CONTROL OF HEMOGLOBIN POLYPEPTIDE CHAIN SYNTHESIS

In this discussion it will be assumed that normal adult and fetal human hemoglobins each have a unique amino acid sequence. The molecules consist of two identical halves, as shown by X-ray crystallography (see Kendrew and Perutz, 1957). In each half of the molecule there are two different polypeptide chains, α and β, which are characterized by the N-terminal amino-acid sequences valine leucine- and valine histidine leucine-, respectively. Recently (Hunt, 1959) it has been shown that human fetal hemoglobin (HbF) has two α chains identical with those in HbA and two other chains, that can be termed γ, having N-terminal glycine (Schroeder and Matsuda, 1958).

An attempt will now be made to provide an explanation for the genetic control of hemoglobin synthesis (see Figure 1). Evidence has accumulated that the genes for the abnormal hemoglobins G and Hopkins 2 (Ho2) are inherited independently of the sickle-cell gene (Schwartz, Spaet, Zuelzer, Neel, Robinson and Kaufman, 1957; Smith and Torbert, 1958). This implies that more than one locus is concerned in hemoglobin synthesis, and the simplest inference is that each of two loci controls the formation of one polypeptide chain. The genes controlling the synthesis of normal α, β and γ chains can be termed $Hb\alpha^A$, $Hb\beta^A$ and $Hb\gamma^F$, respectively (Figure 1).

The sickle-cell and hemoglobin C molecules differ from the normal molecule at the same site, which must lie in the β-chain since it does not affect HbF. The Dβ and E hemoglobins differ from HbA in the same chain as S and C, whereas the Dα and I mutations differ from HbA in the other chain (Ingram, 1959).

The normal individual may therefore be designated $Hb\alpha^A/Hb\alpha^A$, $Hb\beta^A/Hb\beta^A$,

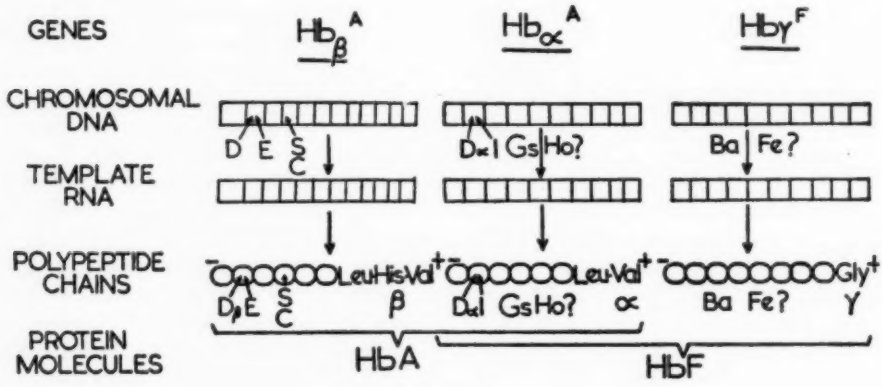

FIGURE 1

Diagram of the supposed relationships between the hemoglobin genes and the proteins whose synthesis they control. The arrows indicate the position of the changes in chromosomal DNA and polypeptide chains involved in mutations. Thus, S and C affect the same amino-acid, D and E the same peptide but not necessarily the same amino-acid. However, it is not meant to imply that the latter peptide is closer to the N-terminal than the peptide involved in the S and C mutation. Hemoglobin G_s is the G of Schwartz *et al.*

$Hb\gamma^F/Hb\gamma^F$, the carrier of the sickle-cell trait $Hb\alpha^A/Hb\alpha^A$, $Hb\beta^A/Hb\beta^S$, $Hb\gamma^F/Hb\gamma^F$, the carrier of the hemoglobin I train $Hb\alpha^A/Hb\alpha^I$, $Hb\beta^A/Hb\beta^A$, $Hb\gamma^F/Hb\gamma^F$, and so forth.

Evidence consistent with this hypothesis has been obtained by recombination of dissociated molecules (Singer and Itano, 1959; Itano and Singer, 1959; and unpublished observations of the author). It has been known for some years that under mildly acidic conditions HbA breaks down into half-molecules. Recent evidence has shown that this is an asymmetric process, the subunits containing $\alpha\alpha$ and $\beta\beta$ chains, respectively. When mixtures of A + S, A + C and S + C hemoglobins are allowed to dissociate, the subunits are exchanged, but the molecules retain their original charge (Figure 2). When mixtures of S or C and I or Hopkins 2 hemoglobins are allowed to dissociate and recombine, however, approximately one-fourth of HbA is formed, along with a hybrid abnormal molecule (Figure 2). This is the result expected if the abnormalities in the S and C molecules on the one hand, and the I and Ho2 molecules on the other, are located in different polypeptide chains. A subject with S and Ho2 hemoglobins described by Smith and Torbert (1957) was found to have HbA, which suggests that the hemoglobin polypeptide chains are synthesized independently and recombine at random in the erythrocyte precursors.

The older dogma of "one gene, one enzyme" can now be replaced by "one cistron, one polypeptide chain." The interpretation given above of the genetic control of hemoglobin synthesis leads to certain verifiable predictions. Thus, when abnormal forms of foetal hemoglobin are replaced by normal adult hemoglobins (Fessas and Papaspyron, 1957; Ager and Lehmann, 1958) the abnormality should lie in the γ chain. And adult hemoglobin variants such as $D\alpha$, I and Hopkins 2 with abnormal α chains

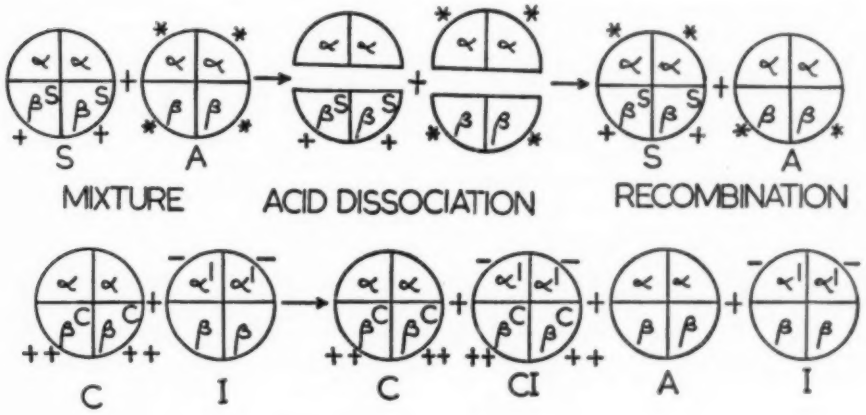

FIGURE 2

Diagram showing the recombination of hemoglobins dissociated into half-molecules by acid. The asterisk shows transfer of a radioactive label. The + and − signs represent differences in electric charge from HbA polypeptide chains.

should be accompanied by abnormal fetal forms. Verification of these predictions would be additional evidence in favor of the hypothesis.

POPULATION GENETICS OF ABNORMAL HEMOGLOBINS

When a major gene mutates, the new allele is generally disadvantageous. The reasons for this are sufficiently obvious. Mutations are random changes relative to the needs of the organism, and when they occur in any highly organized system, such as the human body, they are more likely to be harmful than useful. Occasional mutations are advantageous and then the mutant genes spread through populations, replacing the original genes at the loci concerned. This process has actually been witnessed in populations of insects and microorganisms. Thus, during the past fifty years melanic mutants of many species of moths have become common in industrial areas because they are better camouflaged and less subject to predation than the original forms (Ford, 1956). The spread of insects resistant to DDT and other chemicals, and of bacteria resistant to drugs, has been reviewed by Crow (1957). These are dramatic examples of changes in the genetic composition of natural populations of organisms in response to powerful selective agencies.

In other circumstances the spread of a mutant gene which is initially advantageous is checked at a certain point, so that both the mutant and the original gene persist in the population indefinitely. This is the situation known as polymorphism. As Fisher (1930) showed, it will arise when subjects heterozygous for two genes are favored by selection over both homozygotes.

One of the best examples is provided by the sickle-cell gene which has remained common in parts of Africa and elsewhere despite the fact homozygotes develop a severe anemia from which most die in childhood. Allison (1954a) recognized that the trait is common only where malaria is hyperendemic. He was able to show (1954b) that children carrying the sickle-cell trait are resistant to malignant tertian malaria, so that they stand a better chance of surviving through the dangerous years of first exposure to the disease—before immunity is built up—than children without the trait. There is now substantial evidence that this view is correct (Allison, 1957; Vandepitte and Delaisse, 1958; Raper, 1959).

It is therefore justifiable to conclude that the sickle-cell gene—initially a rare mutant — has been favored by natural selection in malarious areas, so that it has increased in frequency until the advantage of the heterozygote is counterbalanced by the disadvantage of the homozygote, after which it has remained relatively constant. High frequencies of the sickle-cell trait have been recorded in malarious parts of Africa, Sicily, Greece, Southern Turkey, Southern Arabia and India. The incidence of the trait in some African tribes is about 40 per cent, which implies that the sickle-cell heterozygote has about a 25 per cent better chance of reproducing than the normal homozygote. If the environment were to change in such a way that the advantage of the sickle-cell heterozygote were eliminated, the frequency of the sickle-cell gene would be expected to fall. This may well have happened within three centuries in the Negro population of the United States, amongst whom the frequency of the sickle-cell gene (4 per cent) is now considerably lower than

expected from their African ancestry even when allowance is made for white and Indian admixture.

Because of the magnitude of the selective forces involved, it has been possible to demonstrate the effects of selection in another way. Allison (1956) found that in populations of African infants tested at an age prior to mortality from sickle-cell disease and malaria, the ratios of the three genotypes were close to those expected from the random mating hypothesis. However, in the parental population there was a significant excess of sickle-cell heterozygotes and deficiency of sickle-cell homozygotes. This is direct evidence that the heterozygotes have a greater chance of surviving to reproductive age than other genotypes. Confirmatory observations from the Belgian Congo have been published by Vandepitte and Delaisse (1958).

An interesting complication is introduced into the situation in West Africa, where the hemoglobin C gene is common. The tendency for sickle-cell and hemoglobin C molecules to form mixed aggregates produces a well-known variant of sickle-cell disease in subjects who inherit a sickle-cell gene from one parent and a hemoglobin C gene from the other parent. This syndrome was described by Kaplan, Zuelzer and Neel (1951) and numerous cases have been reported from the United States and West Africa. More than one per cent of children born in Ghana have hemoglobin C : sickle-cell disease. Allison (1955) postulated that because of the disadvantageous effects of the sickle-cell and hemoglobin C genes in combination, the two genes must tend to be mutually exclusive in populations. This was subsequently found to be the case. Hemoglobin C is present in all West African territories, the incidence of heterozygotes rising to 29 per cent in northern Ghana, and as the frequency of hemoglobin C increases that of the sickle-cell trait falls (Allison, 1956; Edington and Lehmann, 1956). An apparent exception occurred among Liberians, who were reported to have low frequencies of both the sickle-cell and hemoglobin C genes. However, the recent demonstration of a relatively high frequency of carriers of thalassemia in the population (Olesen *et al.*, 1959) provides an explanation for the low frequency of the other genes, which are known to be disadvantageous in combination with thalassemia.

Thus powerful selective forces appear to have stabilized the frequencies of the abnormal hemoglobin genes in complex genetic equilibria in West Africa. The same sort of situation almost certainly obtains in other human populations in which the genes for abnormal hemoglobins are common. Among many Mediterranean peoples the thalassemia trait has persisted in frequencies up to 20 per cent although the homozygous condition is nearly always lethal. In several South East Asian countries, such as Burma, Thailand and Indonesia, the genes for hemoglobin E, thalassemia and hemoglobin H are all common despite the fact that individuals who inherit two abnormal genes are liable to hemolytic anemias of varying degrees of severity. The most plausible inference is that the possession of a single abnormal gene is advantageous, but the selective agencies involved have not yet been investigated.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY IN ERYTHROCYTES

It has been known for several years that some individuals of Negro, Mediter-

ranean or East Indian origin are liable to hemolysis when given therapeutic doses of the antimalarial primaquine and other drugs. The sensitivity was shown by Beutler and his colleagues (see Beutler, 1959) to be due to a specific defect in erythrocytes. The most striking change, and possibly the primary genetic defect, is reduction in activity of the enzyme glucose-6-phosphate dehydrogenase (Carson *et al.*, 1956). Associated with this is "glutathione instability"—diminution in the amount of reduced glutathione in cells incubated with acetylphenylhydrazine. The trait appears to be sex-linked with full expression in male hemizygotes and variable expression in female heterozygotes (see Childs *et al.*, 1958). This trait is also responsible for "favism," a severe hemolytic diathesis produced in sensitive subjects (usually in Mediterranean countries) following ingestion of fava beans. Hence there is reason to believe that the trait is potentially harmful, despite which it has attained high frequencies (up to 30 per cent) in some human populations. The possibility that the trait is protective against malaria again arises, as Motulsky and Campbell (1959) have recently emphasized. The distribution of the trait certainly corresponds remarkably well with that of malignant tertian malaria, and the malaria parasites are known to require reduced glutathione for growth. The sex-linkage makes the polymorphism of general interest, for it might be maintained by advantage of the male hemizygote alone, although recent theoretical studies suggest that some advantage of female heterozygotes is also required (Mandel, 1959).

OTHER SERUM PROTEIN POLYMORPHISMS IN MAN

Three sets of genetically controlled differences in human serum proteins have recently been analyzed. They concern different proteins and appear to be inherited quite independently of one another. The first affects the haptoglobins, serum proteins that have the specific property of combining with hemoglobin. Smithies (1955), using electrophoresis with starch gels as supporting medium, showed that the sera of normal subjects fall into three groups. It has since become clear that the determinant proteins are haptoglobins, and the sera are now referred to as type 1-1, 2-1 and 2-2. The mode of inheritance of the three types suggests that they are controlled by a single pair of allelic genes, Hp^1 and Hp^2 (Smithies and Walker, 1956); there are, however, exceptions mentioned by Allison (1959a). In type 1-1 a single haptoglobin component is seen, but in types 2-1 and 2-2 numerous haptoglobins bands, characteristic of the two types, are seen on starch gel electrophoresis of sera. This system is of unusual interest in relation to the genetic control of protein synthesis, for not only does the heterozygous individual produce proteins different from those in either homozygous type, but also in two of the types the haptoglobins consist of several fractions. No other genetic system is known in which a single locus controls the specificity of more than one protein (Allison, 1959b). The difficulty has been resolved by the demonstration that the type 1-1 haptoglobin is a monomer while in the other two types the haptoglobins form a series of polymers (Allison, 1959c). One other observation is of interest. A relatively high proportion of Africans lack demonstrable haptoglobins. This is likely to be a congenital lack in at least some cases, since it has been observed also in American Negroes (Giblett, 1959). The absence of

haptoglobins in Africans is remarkable from the point of view of population genetics. The individuals concerned must have recurrent hemoglobinemia from malaria in childhood, which in the absence of haptoglobins would be expected to lead to significant iron and protein depletion (haptoglobins prevent loss of hemoglobin in the body through the urine). Hence one would deduce that the absence of haptoglobins would be disadvantageous, in spite of which the trait remains remarkably common. The simplest explanation is that persons heterozygous for the factor concerned are favored by selection. At present we do not know even where to direct our search for such an advantage.

The second group of serum proteins showing genetically controlled variation are the beta-globulins binding iron, the transferrins. Several transferrin types differing in electrophoretic mobility have been described. Both the normal and the abnormal molecules can carry iron, and they are closely related antigenically (Smithies, 1959; Allison, 1959d). The molecules may differ from one another only in small details of structure, as in the case of the hemoglobin types. Genetically controlled variation in gamma-globins has also been described on the basis of serological tests (see Harboe and Lundervall, 1959) but has not been defined chemically.

ABNORMAL HEMOGLOBINS AS A WORLD PROBLEM

In large areas of Central Africa, from Tanganyika in the East to Sierra Leone in the West, the sickle-cell trait is present in most tribes in frequencies of the order of 20 per cent. About 1 per cent of children born have sickle-cell disease, the incidence rising to 4 per cent where the sickle-cell trait frequency is at its upper limit of about 40 per cent. In many Mediterranean populations the frequency of thalassemia trait is of the order of 10 per cent, rising to 20 per cent in some places. On an average about one child in 400 born in these areas has thalassemia major. Both the thalassemia and hemoglobin E genes are common in South East Asia, the frequency of the latter rising to above 20 per cent in Thailand. It is likely that about 1 per cent of children in this whole region will be born with susceptibility to hemolytic disease—either through homozygosity for an abnormal hemoglobin gene or double heterozygosity for two (thalassemia and hemoglobin E). So there is no doubt that the abnormal hemoglobins present a world problem of considerable magnitude, many millions of people carrying the genes concerned.

Two general conclusions are of interest from the eugenic point of view. In the first place it is clearly undesirable for two persons carrying abnormal hemoglobin genes to have children. One child out of four would inherit the predisposition to a chronic and painful disease. And the widespread dissemination of this knowledge among susceptible populations who are sufficiently educated to understand its implications seems worth while. However, the possibility of obtaining co-operation in this respect among the majority of the African and Asian populations concerned seems small. The second point is that in societies with adequate medical care the frequency of abnormal hemoglobin genes should gradually fall—unlike genes predisposing subjects to diabetes mellitus and some other conditions which will gradually accumulate.

The question arises whether there is any hopeful prospect of treatment of inherited anemias. The answer to this at present seems to be in the negative. There is clearly no possibility of simple substitution therapy like that of insulin in diabetes mellitus and thyroid hormones in hypothyroidism. One possibility—at present only of theoretical interest—remains, that of substituting normal erythrocyte precursors for the abnormal ones in inherited anemias. Work of this kind has already been successfully undertaken in experimental animals. Russell, Bernstein and Smith (1958) have used mice carrying deleterious genes of the *W*-series which in double dose produce a severe macrocytic anemia. Anemic animals were irradiated to destroy their red cell precursors and given injections of normal (*w*/*w*) cells. The donor cells survived for long periods and functioned normally when the donors were from the same inbred strain of mice (isologous implantation). In a high proportion of cases isologous implantation was successful even without prior irradiation. However, homologous implantations (from unrelated mice) were unsuccessful. This is the rub from the point of view of application to human subjects, since implantations would always have to be homologous. Not only is there a danger of an immunological reaction of the host against the graft, but also of a reaction of the graft against the host producing "secondary disease" (see Medawar, 1958). One possibility is giving newborn children with hereditary anemias repeated injections of foreign normal human hemopoetic tissue. In this way it has been possible to induce, for example, tolerance in rats to foreign erythrocytes (Nossall, 1958). The degree of "immunological maturity" of the newborn human, and whether tolerance to foreign antigens can be induced, is still unknown, however.

The whole question of homologous implantations of bone-marrow cells in man is at present under intensive study, both from the point of view of treating subjects who are severely anemic after irradiation and in attempts to destroy leukemic cells by irradiation and substitute normal cells. The results will be watched with considerable interest, since on general grounds it is likely that implantations of normal blood-forming tissue would be at a competitive advantage against sickle-cell or thalassemic blood-forming tissue whereas they would be at a competitive disadvantage against fast-growing leukemic tissue.

At present, only general measures can be adopted, such as giving blood transfusions and making sure that subjects with sickle-cell disease avoid general or local deoxygenation. Thus, individuals with sickle-cell disease or any of its genetic variants should not fly in aircraft at all, and sickle-cell trait carriers should not fly at high altitudes in unpressurized aircraft. Since about 8 per cent of American Negroes have the trait, this represents a military problem to which due attention is being given. And any situation that would lead to acidity of erythrocytes, which promotes deoxygenation and sickling, should be avoided.

In general, the spectacular progress has been made in the recognition and study of biochemical differences in hemoglobin types, serum protein types and other characters in the last few years (see Allison, 1959b) is likely to continue as refined methods of analysis are applied to more and more bodily constituents. Already an enormous amount of chemical variability has been revealed—and also antigenic variability—which will at

some stage be amenable to chemical definition. The uniqueness of the individual's chemical constitution is reflected in the reaction against homografts, which are tolerated only between uniovular twins or among highly inbred animals (Medawar, 1958).

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A NEW HEREDITY COUNSELING SERVICE IN WESTERN CANADA

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THE HEREDITY COUNSELING SERVICE of the University of Alberta Faculty of Medicine, set up in 1957, is the first service for counseling in human genetics in Western Canada. Its establishment came about as a natural outgrowth of teaching and research in human genetics in the University, in accordance with the University's tradition of service to its community. It has been well received; at present, just two years after its inception, an average of ten cases a month are referred to it for genetic assessment. Some account of its background, operation, difficulties, and prospects may be of interest to other workers in the field of applied human genetics.

Alberta has a population of just over a million people and an area of a quarter of a million square miles. The population is more concentrated than these figures suggest, however; only the southern half and the northwestern Peace River Block are really settled, and almost half the total population is concentrated in the two cities of Edmonton and Calgary. The 1200-bed University Hospital in Edmonton is a referral center for the whole province.

To a human geneticist, Alberta's population presents some unusual genetic aspects, particularly because of its mixed ethnic origin and its recent settlement. Settlement of the province followed upon the completion of the transcontinental Canadian Pacific Railway in 1885. The settlers came mainly from older parts of Canada and the United States, the British Isles, Germany, and the Ukraine. There are about 20,000 native Indians and Métis, most of whom live on reservations as wards of the Federal Government.

A striking illustration of the newness and the rapidly changing character of Alberta's population is provided by the changing proportion of University of Alberta students born in the province. According to the records of the Registrar's Office of the University, in 1913-14 only 7.6 per cent of the University students were Alberta-born; in 1933-34 the 50 per cent mark was passed; and by 1953-54, the most recent year for which these figures have been compiled, the percentage of Alberta-born students was 73.9.

The breeding structure of the Alberta population is far from random. Particularly during the early years of settlement, small isolates developed, usually formed by groups who had come at the same time from the same homeland, shared the same religious beliefs, and may well have already been somewhat inbred. The Hutterite colonies form the most striking remaining example of these isolates. More recently, in contrast with

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the former tendency to form isolates, wide out-breeding has become common. Inspection of the marriage column of any Alberta daily paper will show that marriages between people of rather dissimilar origin (especially between those of Eastern European and those of Western European parentage, as indicated by surnames) are increasingly common among young Albertans. Usually, couples who seek counseling do not know whether or not their parents are consanguineous, although the geographic origin of the parents may make consanguinity seem probable.

Another unusual feature of the local scene in relation to human genetics is that Alberta is the only Canadian province to have and to enforce a so-called "eugenics law." Under this law, passed in 1928 during what Neel and Schull (1) have called "the first flush of eugenic enthusiasm," compulsory sterilization can be performed for Huntington's chorea, epilepsy with psychosis and mental deterioration, neurosyphilis, and mental defect where in the opinion of the Eugenics Board the condition is hereditary or involves the risk of mental injury to the patient or to his progeny. During 1957, 82 sterilizations were performed under the Act. Furthermore, as is customary elsewhere also, the major hospitals have "eugenics committees" to consider cases for voluntary sterilization. The decisions of the Eugenics Board and eugenics committees seem to be determined more often by medical and sociological than by genetical considerations.

At the 1954 Teaching Institute of the Association of American Medical Colleges, the value of genetics in medical education received recognition. Immediately thereafter, in the spring term of 1955, Alberta became one of the first medical schools in the country to add a formal course in human genetics to the medical curriculum. (This development was facilitated because a trained human geneticist was already present on the campus as a part-time physiologist and faculty wife. In the present shortage of human geneticists, Alberta may be the only university to have found staff readily available when required).

Two years later, because it was obvious that many physicians and social agencies in the province would find it convenient to have a center to which genetical problems encountered in daily practice could be referred, the Heredity Counseling Service was instituted. The Service is under the guidance of five clinical departments: Medicine, Preventive Medicine, Paediatrics, Obstetrics and Psychiatry. The heads of these departments, with the human geneticist, form the Heredity Counseling Committee of the Faculty of Medicine. The affiliation is with the University rather than the University Hospital so that the Service will be accessible to as wide a group as possible, but most of the counseling so far has been done in and for the University Hospital. In order to prevent improper use of the Service, it is required that cases be referred by physicians or by agencies such as the Department of Child Welfare of the provincial government; this was decided on the advice of an original Committee member who had had experience with British heredity clinics which were open to the general public. Financial support has been provided by a Federal-Provincial Public Health Grant, and at present no fees are charged, although the decision not to charge fees was reached against the advice of some of the clinical members of the Committee and may be changed later. Cases in which heredity counsel-

ing is requested are referred to the chairman, who can then discuss the clinical and genetical aspects with the appropriate clinical member of the Committee if necessary. The referring physician may request that only he, and not the patient, receive a report; this frequently happens in cases of, for example, dermatoglyphic diagnosis of mongolism, but only rarely except when our assistance is primarily for diagnostic purposes.

We find it necessary, for reasons of medical ethics, to accept the diagnosis provided by the referring physician, even when its accuracy is doubtful; for example, if a patient is sent in for heredity counseling as a case of muscular dystrophy, and if the family history does not contradict this diagnosis, we feel we must base the genetical opinion upon it even though it may be incorrect. This presents a real difficulty, potentially at least. Fortunately it is not always necessary to have an accurate diagnosis in order to identify a hereditary pattern. Nevertheless, cases in which the diagnosis is obscure have been the least satisfactory to deal with; no doubt this statement is even more true to a medical practitioner.

The types of problems sent to us are varied and undoubtedly depend to a great extent upon the research interests of the counselor and her colleagues. The most common type of problem is that of the probability of a second abnormal child in a family in which one such child has already appeared; this seems to be the most common kind of case in every heredity counseling center. A particularly large number of requests come to us for dermatoglyphic diagnosis of mongolism, especially in cases where a difference of opinion exists. Dermal pattern analysis is not truly genetic counseling, but no one else in Alberta provides this particular service and we are glad to do so. There are fairly frequent requests for diagnosis of chromatin positivity or negativity, formerly termed "nuclear sex"; these are referred in turn to an anatomist who is interested in the technique and its applications. We suspect that the recent advances in human cytogenetics (2) will have some effect upon the types of problems submitted. Recently the number of requests for preadoption counseling has risen; such requests have come from both adoption agencies and adopting parents. Premarital counseling, at least in a formal way, does not make up a large proportion of our work; as any geneticist who teaches University students knows, premarital counseling most often takes place at the end of a lecture or during a lull in a laboratory period, when a student sidles up embarrassedly and says, for example, "My girl friend is Rh negative; should I give her up?" These inquiries, though they have their comical aspects, are desperately serious to the young people involved and deserve to be treated seriously. Consanguinity is rare as a counseling problem in Alberta. Finally, certain cases are referred either because the genetical picture may be required as a diagnostic aid, or primarily for the purpose of broadening the geneticist's experience ("Have you ever seen a case of Leber's optic atrophy? Well, go and talk to Mr. X on Station 99.")

Whether or not it is proper to give advice by mail is a controversial subject among heredity counselors. (3) Many inquiries come to us from rural practitioners whose training did not include medical genetics and who are distant from medical libraries. There is certainly nothing questionable about looking up the appropriate information and sending it, complete with references, to the

inquirer. Our regulation that cases be referred by a physician spares us the necessity of providing this service to the general public.

The value of the Heredity Counseling Service to the medical profession and to Alberta citizen is best measured by its steadily increasing case load. It has also assisted greatly in promoting the development of human genetics in the University of Alberta, because we receive so much interesting material that would otherwise be lost. The geneticist has gained much experience because of the wide variety of the referrals. Almost all teaching examples used can now be taken from the Heredity Counseling Service files, and, in research, several family histories have been well worth further investigation.

We expect that, as time goes on, an increasingly large proportion of the province's physicians will be able to recognize and to handle genetical problems themselves, and that the Heredity Counseling Service will then receive only the more complicated types of cases as referrals. We also anticipate that "eugenics committees" will become in fact what they are now in name, and will develop a more sophisticated approach to the problems of eugenical sterilization. Furthermore, we hope that with the expansion of our understanding of human genetics, particularly in the areas of detection of carriers, empiric risk figures, and the interrelation between genetical and environmental factors in development, we will be able to be increasingly helpful to the people who seek our advice.

The small beginning that has been made in heredity counseling in Alberta has been described. It is a pleasure to report, in closing, that two of the other three Western Canadian universities now have, or soon will have, human geneticists on their staffs. It is obvious that our science is receiving increasingly wide recognition and that the institution of a heredity counseling service here has been only one instance of the increasing recognition of human genetics as an indispensable means of widening man's understanding of his own nature.

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MARRIAGE AND FERTILITY PATTERNS OF COLLEGE GRADUATES*

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FOR ELEVEN YEARS the Population Reference Bureau undertook annual surveys of college graduates of 10-year and 25-year standing. These surveys, conducted from 1946 through 1956, were designed to measure trends in the fertility of college-educated persons. The graduates of 25 years previous would have virtually completed their families, whereas the graduates of only 10 years standing would be about midway through their most fertile years.

STUDY PROCEDURES

The universe from which the sample was drawn consisted of all the colleges with a reported enrollment of 500 or more students as listed in the *Education Directory* published annually by the U.S. Office of Education. It was a self-selected sample in that it consisted of all the colleges which indicated their willingness to cooperate. Each fall, letters were sent to the listed colleges—to the sociology departments, alumni offices, or presidents—requesting their participation in the Study for that year.

A mail questionnaire was deemed to be the most effective and practical method of contacting the graduates to be studied—those that had graduated 10 and 25 years previous from the colleges which had indicated they wished to cooperate. Because of the limited office personnel and financial resources of the Study, the mailing of the questionnaires was to be done by the colleges in conjunction with their own mailings of literature to their 10-year and 25-year graduates. The brief post-card questionnaire included questions on the year of graduation, whether or not the graduate had ever been married and, if so, the number of children he (or she) had ever had. The 1955 and 1956 questionnaires were expanded to include, for ever-married graduates, the (calendar) year of marriage and the (calendar) year of birth of each child up to the fifth. The colleges tallied the results and returned the report forms to the Study office.

On the average, almost 145 colleges participated each year in the College Study. The highest participation occurred in 1950 and 1951 when about 200 colleges and universities cooperated. For five other years, the number of colleges ranged between 159 and 179. The participation was lowest for the first three years of the Study and the last year, when less than 100 colleges in each year cooperated.

The reasons for these fluctuations in the number of participating colleges are not specifically known. It is probable, however, that whether or not a college participated depended largely upon the workload and staff availability of the college alumni office or sociology depart-

*Paper presented at the Annual Meeting of the Population Association of America, Providence, Rhode Island, April 26, 1959.

ment when the requesting letter was received. Also, for some colleges, the decision regarding participation may have been influenced by the emphasis which the Study placed on the eugenic implications of the fertility of college graduates. In any event, a study was undertaken of the influence, if any, of the variable participation of colleges on the data. No large differences were observed between the data for the group of colleges which had participated in the Study for most of the survey years and the total colleges in any given year. Thus it appears that any bias resulting from the changing participation of colleges from year to year has little significance.

As the coverage of colleges varied considerably from year to year, so also did the number of responding graduates. Survey year 1950 had the largest number of participating colleges and graduates available to the Study—those with known address—almost 50,000 (Table 1). The year following the inception of the Study, 1947, shows the lowest number of colleges and graduates. Between 1948 and 1954, the number of graduates available to the Study each year exceeded 30,000.

The response rate has been over 50 per cent for every year, reaching a peak in 1954 and 1955 when 75 per cent of the graduates returned the questionnaires. The lowest response rate, 59 per cent, occurred in the 1956 survey, when the number of participating colleges and graduates available to the survey were also low. Discussing this, the Bureau points out that the low response rate and the small number of colleges were probably attributable to four factors: (1) Some revisions in procedures, (2) delays incident to the reorganization of the Study which may have caused some of the colleges not to follow up the initial mailing as thoroughly as before, (3) war service which greatly reduced the number of male graduates in the class of 1946, and (4) a change in the questionnaire which some colleges interpreted so rigidly that questionnaires were sent only to graduates with a B.A. degree.

MAJOR FINDINGS

Table 1 summarizes the major findings of the 11 surveys which were conducted. The data reveal two important trends: (1) For both the older and younger graduates, male fertility was consistently higher than female fertility; (2) the younger women, 10 years after graduation, had already had a higher average number of children than the older women, 25 years after graduation. This latter trend first started to become evident in 1951 among all graduate women. By 1956, the difference between the older and younger women graduates was 15 children per 100 graduates.

Increases in fertility occurred among all four groups of graduates during the period the College Study was conducted. The increase among male graduates was greater than that among female graduates for both the younger and the older groups. However, for both sexes, the fertility of the younger graduates increased more than that of the older. The older men reported an increase of 34 children per 100 graduates, whereas the older women reported an increase of only 12 children per 100 graduates. Among the younger men, the number rose from 102 children per 100 graduates to 190, an increase of 88 children per 100 graduates, and the women reported an increase of 75 children per 100 graduates, from 95 per 100 in 1946 to 170 in the 1956 survey. Increases in marital fertility were of just about the same magnitude.

TABLE 1

TOTAL GRADUATES, PER CENT EVER MARRIED, AND NUMBER OF CHILDREN EVER BORN PER 100 GRADUATES BY MARITAL STATUS, BY SEX: 25-YEAR AND 10-YEAR GRADUATES

Survey year	*25-Year Graduates*					*10-Year Graduates*				
				Children ever born					Children ever born	
	Class	Total graduates[1]	% ever married[2]	Per 100 graduates[2]	Per 100 ever married graduates[2]	Class	Total graduates[1]	% ever married[2]	Per 100 graduates[2]	Per 100 ever married graduates[2]
					MEN					
1946	1921	4,473	94	175	187	1936	6,052	88	102	123
1947	1922	2,884	92	170	185	1937	5,453	83	111	133
1948	1923	6,454	93	176	189	1938	11,885	85	121	144
1949	1924	6,854	96	177	184	1939	12,470	91	137	151
1950	1925	10,000	95	181	190	1940	20,487	89	140	157
1951	1926	8,609	94	184	196	1941	16,528	87	142	164
1952	1927	7,272	94	185	198	1942	12,420	89	151	170
1953	1928	8,685	94	197	210	1943	11,521	88	163	184
1954	1929	8,832	93	195	209	1944	5,675	88	170	195
1955	1930	8,140	94	197	209	1945	4,704	89	173	195
1956	1931	4,265	95	209	220	1946	3,663	90	190	212
					WOMEN					
1946	1921	2,987	80	143	179	1936	5,102	77	95	123
1947	1922	2,360	75	136	181	1937	3,827	73	106	144
1948	1923	4,590	74	123	166	1938	7,223	74	110	148
1949	1924	6,107	73	126	173	1939	10,091	73	111	153
1950	1925	6,849	73	123	170	1940	12,294	73	115	157
1951	1926	6,609	71	118	166	1941	10,159	74	119	161
1952	1927	6,763	72	119	165	1942	9,869	75	123	163
1953	1928	7,507	72	124	173	1943	10,150	74	130	176
1954	1929	7,328	74	136	182	1944	8,857	75	139	184
1955	1930	7,689	77	136	177	1945	8,961	77	143	184
1956	1931	4,602	82	155	190	1946	6,106	85	170	199

[1]Graduates with known address
[2]Based on graduates reporting

The proportions married among the various groups of graduates remained virtually constant during the 11 years the Study was conducted, except among women in the 1956 survey. Among the older men, the proportion ever married varied by only 4 percentage points, between 92 per cent for the graduates of 1922 and 96 per cent for the graduates of 1924. There was somewhat greater variation among the younger men in that the graduates of 1937 reported 83 per cent ever married and the graduates of 1939 reported 91 per cent ever married.

For women, on the other hand, the proportion married ranged between 71 and 80 per cent for the older graduates and between 73 and 77 per cent for the younger graduates. In 1956, both groups reported much higher proportions married—82 and 85 per cent, respectively. These higher proportions are probably due in large part to a procedural change in the Study inaugurated in 1956. Prior to that year, questionnaires had been mailed to all the men graduates but only to married women graduates; i.e., those designated as "Mrs." on the alumnae records. In 1956, questionnaires were sent to all women graduates with known address. This change was made for two reasons: (1) Some of the women shown as "Miss" on the alumnae records had probably actually married but had neglected to advise the alumnae office, whereas others may have been married, subsequently divorced, and had resumed their maiden names; (2) to make the procedures for men and women similar so that the results for the two sexes would be more comparable. That the procedural change produced the expected result—higher proportions married among the women and, therefore, a lessening of the differential between male and female fertility—is shown by the greater increase for women than men in the proportion reported as married and a reduction in the difference between the number of children per 100 male and female graduates between the 1955 and 1956 surveys. However, the relative size of the change in fertility between the 1955 and 1956 surveys is practically the same for the colleges cooperating in either year as for the smaller number which cooperated in both years.

EVALUATION OF THE STUDY

The College Study data suffer from various inadequacies. The major one is that the sample upon which they are based is not a probability sample so that a direct measure of error or sampling variability cannot be obtained. Secondly, the fact that it was a mail survey is also, to some extent, disadvantageous because only those graduates with known address were available to the Study. Follow-up of nonrespondents was not attempted. A recent study of college graduates in England, which included some follow-up of nonrespondents, shows that the people who do not respond are less often married, more often childless, and less well-off economically.[1] Furthermore, information on various significantly related social and demographic characteristics of the graduates, such as exact age, present marital status, occupation, income, etc., are not available.

It has long been suspected that response to the questionnaire has been related to parenthood, that is, that parents are more likely to return the questionnaire than are childless married graduates and unmarried graduates. A comparison of Census data for college graduates of similar age groups suggests that

[1]Hubback, Judith. "The Fertility of College Women." *Eugenics Review* 47 (2): 107-113. July 1955.

such a bias is inherent in the College Study. However, the College Study data have shown the same general trends in proportions married and children ever born that available Census or national survey data have shown. Furthermore, there is no reason to assume that, to the extent that bias does exist, it would differ from year to year. Therefore, the data are believed to be reasonably reliable and to be comparable between years.

The data presented in Tables 2 to 4 on date of marriage and dates of birth are based on a subsample of the 1955 survey. In 1955, 70 colleges returned 9,343 original questionnaires to the Study office for further analysis. Although only two-fifths of the participating colleges returned the questionnaires, the questionnaires represent about one-half of all the available graduates. However, it must be pointed out that this subsample has inherent in it any biases of the larger sample.

The 1955 survey data relate to the graduates of 1930 and 1945. These groups are of particular interest. The class of 1930 graduated just as the country was entering the Depression years of the 1930's, whereas the class of 1945 graduated as the country was entering a period of prosperity following World War II. Because social and economic conditions differed during the years immediately succeeding the graduation of these classes, and since the fertility of the group as a whole is controlled, differences between these two specific graduating classes are to be expected. However, it is interesting to note that probbably most of the men who graduated in 1945 were those who had been rejected for physical unfitness by the Army during the war years. It is regrettable that data for a more "normal" group are not also available for purposes of comparison.

The analysis to be presented here is limited to the experience of the graduates of 1930 and 1945 during the ten years immediately succeeding their graduation from college. Direct comparisons of the total fertility of the two graduate groups cannot be made at this time since the graduates of 1945 still had at least 10 to 15 years of reproductive capacity before them when they were surveyed in 1955. On the other hand, the graduates of 1930 had virtually completed their fertility by the time of the survey.

ANNUAL FIRST MARRIAGE RATES

Table 2 presents annual first marriage rates for the ten years immediately following graduation for the graduates of 1930 and 1945 by sex. Although the questionnaire did not specifically ask for date of first marriage, as opposed to current marriage, the question read, "Have you ever married?" If yes, a space was provided for insertion of the date. Thus, it was assumed that in most cases the date of marriage obtained relates to first marriage. This assumption is further substantiated in that no graduates reporting on children reported the date

TABLE 2

ANNUAL FIRST MARRIAGE RATES PER 1,000 GRADUATES SUBJECT TO FIRST MARRIAGE, BY SEX: GRADUATES OF 1930 AND 1945

Graduates of 1930			*Graduates of* 1945		
Year	Men	Women	Year	Men	Women
1930	76	81	1945	113	154
1931	94	103	1946	158	255
1932	104	102	1947	207	249
1933	138	135	1948	220	261
1934	184	149	1949	187	209
1935	186	151	1950	230	261
1936	188	151	1951	238	188
1937	168	136	1952	165	186
1938	181	103	1953	207	160
1939	162	103	1954	140	105
1930-1939	801	727	1945-1954	874	898

of birth of the first child as preceding the reported date of marriage.

The important trend that the marriage data show is that during the period 1930-1939, for both men and women, the older graduates married at a slower rate than the younger graduates during the comparable period 1945-1954. The difference for women, however, was more than twice that for men—171 first marriages per 1,000 women during the 10-year period compared to only 73 per 1,000 men. This differential increase for women was great enough to reverse the differential marriage rate of men and women: Among older graduates, the men experienced a higher marriage rate during the 10 years following graduation than the women, whereas among the younger graduates, the women had married faster during the comparable 10-year period than the men. The differential increase in marriage rates among the women probably also accounts for the reversal of the proportion remaining single within 10 years after graduation: Among the older graduates, 27 per cent of the women had never married by 1940 compared to only 20 per cent for the men, whereas the differential among the younger graduates was considerably less and in favor of the women—10 per cent compared to 13 per cent for the men.

For each year, with only two exceptions for the men, the annual first marriage rates were higher for the younger than the older graduates. The greatest differences occurred among the women, between those marrying in 1931 and those in 1946, and those marrying in 1932 compared to 1947. The low rates during 1931-1932 compared to the high rates of 1946-1947 probably reflect the differing economic conditions: 1931 and 1932 were depression years; 1946 and 1947 were post World War II prosperity years.

A comparison of the marriage rates for the two sexes yields interesting results. For the older graduates, although the women experienced slightly higher first marriage rates during the years immediately after graduation, by 1934 the rates for women had become appreciably lower than those for the men. For younger graduates, higher female first marriage rates extended for a longer period of time after graduation, up through 1950. Thus, in both graduate groups, women married at a younger age than men, but the differential is greater among the younger than the older graduates.

ANNUAL BIRTH RATES

Table 3 presents annual birth rates for the four groups of graduates under consideration and birth rates for total native white women in the United States in the appropriate birth cohorts based on Whelpton's cumulative birth rates. The table relates only to births which occurred during the period 1930 to 1939 for the older graduates and women of the 1908-1909 cohorts and those between 1945 and 1954 for the younger graduates and women of the 1923-1924 birth cohorts. Births to total women prior to the periods under study were excluded from the calculations. An adjustment was indicated, but not made, to correct the rates for births prior to 1930 for the cohorts of 1908-1909 and for the births prior to 1945 for the 1923-1924 cohorts. The influence of these early births on the total rates presented here is believed to be negligible.

The most striking feature of Table 3 is the difference between the older and younger graduate groups compared to the older and younger cohorts of total women. For the older group, the birth rates for both men and women graduates

TABLE 3

ANNUAL BIRTH RATES PER 1,000 POPULATION, BY SEX: GRADUATES OF 1930 AND 1945 AND TOTAL WOMEN OF THE 1908-1909 AND 1923-1924 COHORTS

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Graduates of 1930		*Total women born*		*Graduates of* 1945		*Total women born*
Year	Men	Women	1908-1909	Year	Men	Women	1923-1924
1930	1	—	139	1945	4	—	135
1931	24	18	138	1946	42	50	190
1932	33	42	132	1947	60	110	220
1933	46	52	125	1948	109	153	194
1934	71	74	125	1949	169	206	189
1935	93	102	117	1950	223	228	174
1936	109	111	110	1951	214	227	171
1937	126	117	106	1952	258	247	160
1938	135	122	101	1953	222	216	149
1939	145	106	94	1954	233	202	134

Source: Columns (4) and (8) weighted averages calculated from Whelpton, P. K., *Cohort Fertility*. Princeton: Princeton University Press, 1954. Tables A, C, and G (including mimeographed continuation sheets).

continued generally to rise throughout the period 1930-1939. The annual birth rate for total women, on the other hand, starting from a much higher level, declined during the period and was lower than that for both sexes of graduates during the latter part of the 1930's (1937 to 1939).

Among the younger group, fertility increased for both the graduate groups and for total women. Moreover, the birth rate for all women reached a peak in 1947, whereas the birth rates for the graduate groups did not reach their peaks until 1952. For the younger group, also, the birth rate of total women was lower than that of the graduate groups during the latter part of the period, from 1950 to 1954. Thus, during the early years after graduation, the college graduates have their children at a slower rate, but they tend, to some extent, to "catch up" during the later years. This probably, in large part, reflects later age at marriage for college graduates than for all persons.

Table 4 presents parity-specific birth rates for the graduate groups being discussed. In calculating these rates, the population "at risk" in any given year included those persons who had already experienced the immediately preceding event that same year. For example, women married in 1946 were included in the 1946 population "at risk" of a first birth although they may have married so late in that year that it would have been impossible for them to have a first birth during 1946. This was done because the data related only to year of marriage and year of birth, not to month and year of the event.

With few exceptions, the ever-married graduates of 1945 had higher parity-specific rates in each year after graduation than the ever-married graduates of 1930. An interesting exception occurs, however, which may indicate a real difference between the two groups in spacing patterns. First births to zero-parity ever-married men eight and nine years after graduation were higher for the 1930 graduates than for the 1945 graduates. The 1938 rate for the older ever-married men was 208 first births per 1,000 zero-parity graduates. The 1939 rate was 216. For the 1945 ever-married male graduates, on the other hand, the comparable

TABLE 4

ANNUAL PARITY-SPECIFIC BIRTH RATES PER 1,000 EVER-MARRIED GRADUATES, BY SEX: GRADUATES OF 1930 AND 1945

Year	*Graduates of* 1930 1st births to zero-parity persons	2nd births to one-parity persons	3rd births to two-parity persons	Year	*Graduates of* 1945 1st births to zero-parity persons	2nd births to one-parity persons	3rd births to two-parity persons
			MEN				
1930	17.8	—	—	1945	33.1	—	—
1931	141.3	37.0	—	1946	167.9	—	—
1932	136.6	33.1	—	1947	146.5	66.0	—
1933	125.9	89.6	—	1948	214.0	80.0	—
1934	144.9	104.6	105.3	1949	265.1	175.9	64.9
1935	163.0	102.8	115.4	1950	313.4	228.8	74.5
1936	176.1	104.5	102.4	1951	266.1	240.6	130.6
1937	194.4	119.5	87.2	1952	333.3	299.8	131.3
1938	207.6	127.4	61.4	1953	142.2	311.4	115.0
1939	216.0	136.1	85.3	1954	115.9	325.3	185.3
			WOMEN				
1930	5.2	—	—	1945	2.4	—	—
1931	105.3	—	—	1946	136.2	—	—
1932	161.5	50.7	—	1947	217.5	38.6	—
1933	151.0	66.7	—	1948	238.2	130.1	9.2
1934	172.2	84.0	37.0	1949	296.7	167.2	99.3
1935	179.9	152.3	54.7	1950	262.2	255.7	101.1
1936	187.6	135.1	84.6	1951	280.3	256.4	102.4
1937	198.8	143.5	35.5	1952	292.1	265.6	157.0
1938	165.6	179.5	80.0	1953	218.9	261.4	180.7
1939	141.7	141.2	60.2	1954	205.9	266.9	145.2

rates for 1953 and 1954 were 142 and 116 first births per 1,000 zero-parity graduates, respectively. This phenomenon characterizing the older men may reflect the fact that a significant proportion of them waited an exceptionally long time before starting their families. There is no such pattern among the females. Their zero-parity birth rates per ever-married graduate were consistently higher for the younger than the older women for the entire period.

Thus the data show that at least part of the higher fertility of the younger graduates is due to more graduates marrying and having a first child within ten years after graduation. A comparison of the first and second parity birth rates indicates that the higher fertility of the younger groups is also due to higher proportions of first-parity and second-parity graduates going on to have second and third births. This may reflect a real increase in the size of completed families of college graduates. However, all that can be said at this time is that, within ten years after graduation, the graduates of 1945 had had more children than the graduates of 1930.

CONCLUSIONS

In the previous discussion of the limitations of these data it was stated that the sample from which they were obtained was not a probability sample and that, therefore, sampling variability could not be measured. However, the Mann-Whitney U Test, a nonparametric measure, had been used to test whether or not differences between the two graduate groups, males and females separately, are statistically significant. The tests indicate that the older and younger graduate groups differ significantly in

respect to marriage and childbearing.

However, the amount of the bias in the sample cannot be measured. As stated earlier, it appears likely that the graduates who responded to the College Study surveys were more married and had higher fertility than all graduates. Also, graduates of the cooperating colleges may have had larger families than the graduates of other colleges, especially the many colleges enrolling less than 500 students.[2]

With these limitations in mind, the data presented here have shown that the 1945 graduates, within ten years after graduation, had experienced higher marriage and fertility rates than the 1930 graduates during the comparable time period. Many factors, some known and some unknown, brought about the changes. However, given the 1930 depression and World War II prosperity, under conditions of, essentially, controlled fertility, the differences are those which are expected, based on other studies in the field. The extent to which social and psychological factors affected the marriage and fertility patterns of these graduates remain a matter of conjecture.

[2]About half of all colleges enroll less than 500 students.

INTERVALS BETWEEN CONFINEMENTS

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EDITOR'S NOTE:

The December 1958 issue of Eugenics Quarterly *presented a statistical analysis of "Intervals Between Confinements in the Absence of Birth Control" by Louis Henry of the Institut National D'Études Demographiques in France. Mr. Henry's data are subjected to some further analysis in the article that follows by Kumudini Dandekar of the Gokhale Institute of Politics and Economics in India. Louis Henry presented mean intervals between confinements and the internal variance of the intervals. In the article below, Mrs. Dandekar takes as a point of departure the fact "that the striking feature of the data by Louis Henry is the rather small internal variances of intervals between confinements." Her analysis involves estimated subdivisions of the intervals into the periods "before" and "after" the resumption of menstruation. She concludes that the small variances reported by Louis Henry "can be explained only on the assumption of a considerable post-partum sterile period during which not only fecundability but even the probability of renewal of ovulation is zero." It is hoped that the original article by Mr. Henry and the present article by Mrs. Dandekar will stimulate further interest and research in the important but relatively neglected subject of birth intervals.*

In a recent article in this journal, Louis Henry has examined the fertility histories of 50 families. These families had had at least 6 children, and their first 4 intervals between confinements were normal (i.e., the child born at the last previous confinement had lived for at least 12 months). The analysis was based mainly on an examination of the means and variances of the first 4 intervals between confinements for the several families. Four out of the 50 families were rejected from analysis on grounds that, in their cases, the successive intervals showed large internal variances. For the remaining 46 families, the total variance among the recorded 46×4, that is, 184 intervals, was analyzed (by the statistical technique of analysis of variance) into three components: (1) among families, (2) among birth orders and (3) residual. On grounds that the first two components were statistically large in comparison with the third component, it was concluded that the differences between the families and between the birth orders, in the matter of mean intervals, were real and not merely accidental. In other words, it was concluded that (1) some couples were more likely than others to bear children within short intervals and (2) intervals between successive confinements tended to increase with the order of birth.

The purpose of the present paper is to examine the same material from a somewhat different statistical standpoint. For convenience of reference, the basic data are reproduced in Table 1.

As Louis Henry observes: "In the absence of birth control, marital fertility and, hence, intervals between confinements depend mainly on three factors—(1) The woman's fecundability, defined as the probability that she will conceive in the course of one menstrual cycle or, say, within one month. (2) The frequency of uninduced miscarriages and stillbirths, since confinements resulting in live births only are here under consideration. (3) The time lapse between a confinement and the next onset of ovulation." (p. 203) During this period, beginning with a conception and ending with the next onset of ovulation, fecundability is zero. We may therefore refer to this period briefly as the "infecund" period.

These factors may appropriately be made the starting point for a statistical analysis of intervals between confinements. In the following, the first and the third of the above three factors are taken into consideration. The second factor is neglected for want of data.

Let p denote fecundability, namely, the probability that a woman will conceive in the course of one menstrual cycle or say within one month.

Let $P(x)$ denote the probability of an interval of x menstrual cycles or say x months between two successive confinements. Then $P(x)$ is given by the following:

$$P(x) = p(1\text{-}p)^x$$

For a large set of intervals arising out of the same condition of fecundability, the mean and variance of the intervals are given by

$$\text{mean} = 1\text{-}p/p$$
$$\text{variance} = 1\text{-}p/p^2$$

From this it follows that

$$\text{Variance} = \text{mean}\ (1 + \text{mean})$$

Let us examine whether this theoretical relationship between the mean and the variance of the intervals holds good in the observed data. From Table 1, it is obvious that the relation does not hold good. For all the families, either the mean intervals are too large or the variances of the intervals are too small for the relation to hold good. For instance, for family No. 1, the mean interval is 18 so that in accordance with the theoretical relation, the internal variance for this family should have been 18×19, that is, 342. In fact it is only 3. The same is true for all the families. In all cases, the variances are very much smaller than what would accord with the means. Even the family No. 50, which shows an internal variance of above 400, has a mean interval of 34.25 and hence would require the variance to be above 1200.

One reason why the observed variances are too small in comparison with what they should be in accordance with the observed means is that the observed mean intervals are exaggerated. It will be noticed that while deriving the theoretical relationship between the mean and the variance of the intervals, p was defined to be the probability of a woman conceiving in the course of a menstrual cycle. Hence for the theoretical relationship to hold good, the intervals should be considered as beginning from the reappearance of the menstrual cycle after a confinement. In fact, the recorded intervals are measured from one confinement to the next and hence include the infecund period as well. This exaggerates the mean intervals but leaves the

TABLE 1

NORMAL INTERVALS BETWEEN SUCCESSIVE CONFINEMENTS

Women married at Crulai (Normandy) from 1674 to 1742, with at least 6 confinements during the marital life

Families No.	*Interval Between Confinements* (in completed months) 1-2	2-3	3-4	4-5	*Mean Interval* (months)	*Internal Variation* Variance	Standard Deviation (months)
1	17	17	16	20	18	3	1.73
2	33	32	32	29	32	3	1.73
3	20	20	15	18	18.75	5.67	2.39
4	34	34	39	37	36.5	6	2.45
5	16	20	22	18	19.5	6.67	2.58
6	19	23	17	21	20.5	6.67	2.58
7	24	29	25	23	25.75	7	2.65
8	34	30	28	29	30.75	7	2.65
9	14	12	19	17	16	9.67	3.11
10	29	30	25	23	27.25	11	3.33
11	21	17	17	24	20.25	11.67	3.41
12	22	17	26	23	22.5	14	3.74
13	21	24	15	17	19.75	16.33	4.04
14	32	36	26	35	32.75	20.33	4.51
15	25	20	29	30	26.5	20.67	4.54
16	21	20	30	26	24.75	21.67	4.65
17	31	30	40	36	34.75	21.67	4.65
18	14	19	23	26	21	27	5.20
19	15	21	28	23	22.25	29	5.39
20	13	22	21	26	21	29.67	5.45
21	12	19	26	21	20	33.67	5.80
22	20	13	22	27	21	33.67	5.80
23	14	21	28	18	20.75	35	5.92
24	24	34	37	27	31	36.33	6.03
25	15	21	30	23	22.75	38.33	6.19
26	26	24	28	38	29.5	38.67	6.22
27	18	28	18	30	24	41	6.40
28	15	29	25	28	24.75	41	6.40
29	34	35	23	39	33.25	47	6.86
30	38	54	41	42	44.25	49.67	7.05
31	43	31	31	44	37.75	52.33	7.23
32	18	22	35	24	25.25	53	7.28
33	36	31	23	20	28	53.67	7.33
34	32	41	30	46	37.75	57	7.55
35	36	32	31	48	37.25	61	7.81
36	12	30	15	17	19	63	7.94
37	40	25	29	42	34	68.67	8.29
38	15	15	26	32	22.5	71.33	8.45
39	19	24	19	37	25.25	72.33	8.51
40	43	30	22	26	30.75	83	9.11
41	23	42	42	29	34.5	91.33	9.58
42	28	13	36	20	24.75	99	9.95
43	17	40	23	35	29.25	112.33	10.60
44	25	26	32	48	33.25	113	10.63
45	17	28	43	23	28.25	123.67	11.12
46	20	26	24	47	29.75	146.33	12.09
47	13	26	29	53	30.75	278.33	16.68
48	17	19	53	23	28.5	284	16.85
49	16	19	57	43	34.25	386.33	19.65
50	14	45	56	20	34.25	400.33	20.01

variances unchanged. Hence the mean intervals appear too large to be in theoretical relation with the variances.

Under the circumstances, we may make the internal variances to be the basis of further analysis and derive esti-

mates of mean intervals so as to be in true theoretical relationship with the variances. For reasons explained above, such derived mean intervals would be much smaller than the recorded mean intervals. The difference between the two provides estimates of the infecund period, namely, the period beginning with a conception and ending with the next onset of ovulation. In Table 2, we give for the 46 families such derived estimates of mean intervals, estimates of the infecund period and the underlying fecundability, namely, the probability that a woman would conceive within one active menstrual cycle or say the corresponding month.

The most striking feature of Table 2 is the great variation in fecundabilities of different families. This was suggested by Louis Henry in the first of his two conclusions, namely, that some couples were more likely than others to bear children within short intervals. The evidence of the same in the form of estimates of fecundabilities of different families appears more direct. It will be seen that the fecundabilities range from above 0.4 to below 0.08 so that the highest fecundabilities are more than five times as large as the lowest fecundabilities.

The families are also seen to vary in the infecund period following a conception. This period is seen to vary roughly from 15 months to 30 months. It will be noted that the shortest recorded interval between confinements for a family itself provides an estimate of the infecund period. As it is, in a majority of the cases, the estimates of the infecund period based on the internal variances are a little above the shortest recorded intervals. However, the difference between the two is usually very small and the agreement between the two may be regarded as satisfactory. This agreement would improve if two minor computa-

TABLE 2

REDUCED MEAN INTERVALS, INFECUND PERIODS, AND FECUNDABILITIES

Family No.	*Reduced Mean Interval* (months)	*Infecund Period* (months)	*Fecundability p*	*Family No.*	*Reduced Mean Interval* (months)	*Infecund Period* (months)	*Fecundability p*
1	1.30	16.70	.4343	24	5.55	25.45	.1527
2	1.30	30.70	.4343	25	5.71	17.04	.1490
3	1.93	16.82	.3409	26	5.74	23.76	.1484
4	2.00	34.50	.3333	27	5.92	18.08	.1445
5	2.13	17.37	.3194	28	5.92	18.83	.1445
6	2.13	18.37	.3194	29	6.37	26.88	.1356
7	2.19	23.56	.3132	30	6.57	37.68	.1322
8	2.19	28.56	.3132	31	6.75	31.00	.1290
9	2.65	13.35	.2740	32	6.80	18.45	.1283
10	2.85	24.40	.2595	33	6.84	21.16	.1275
11	2.95	17.30	.2530	34	7.07	30.68	.1240
12	3.27	19.23	.2339	35	7.33	29.92	.1201
13	3.57	16.18	.2187	36	7.45	11.55	.1183
14	4.04	28.71	.1986	37	7.80	26.70	.1136
15	4.07	22.43	.1971	38	7.98	14.52	.1113
16	4.18	20.57	.1930	39	8.02	17.23	.1109
17	4.18	30.57	.1930	40	8.62	22.13	.1039
18	4.72	16.28	.1748	41	9.07	25.43	.0993
19	4.91	17.34	.1693	42	9.46	15.29	.0956
20	4.97	16.03	.1675	43	10.11	19.14	.0900
21	5.32	14.68	.1581	44	10.14	23.11	.0898
22	5.32	15.68	.1581	45	10.63	17.62	0860
23	5.44	15.31	.1554	46	11.61	18.14	.0793

tional corrections were adopted. One is in the computation of the mean interval. It is obvious from the manner in which the mean interval is derived from the fecundability that the intervals must be in terms of completed menstrual cycles or months and that the mean must be the mean of such intervals. In the given data, the intervals are recorded in complete months. But while computing the mean interval, half a month has been added to the mean of the intervals in complete months. It seems that this addition of half a month is not appropriate from the standpoint of the theoretical derivation of the mean interval from fecundability. For the purpose of the present analysis, therefore, the recorded mean intervals should be reduced by 0.5. That would reduce the estimate of infecund periods by the same amount and hence bring them in closer agreement with the shortest recorded intervals.

The other correction or rather refinement is in respect of the recording of the intervals. In the given data, the intervals are recorded in terms of complete months. More appropriately they should be recorded in completed menstrual cycles. For obvious reasons this could not be done. But because a menstrual cycle is usually shorter than the month, the intervals would appear numerically somewhat larger if they were recorded in completed menstrual cycles. That would raise the mean interval numerically but would raise the variance still more. For instance, if we take 13 menstrual cycles for every 13 months, the mean would be raised by the factor 13/12 and the variance would be raised by the square of that factor, namely, $(13/12)^2$. This would slightly reduce the estimates of the infecund period and thus bring them in closer agreement with the shortest recorded intervals.

Louis Henry appropriately describes conception as a random process. As he observes, "There is merely a certain probability, called fecundability, that sexual relations will result in a conception. This conception, in turn, has only a certain probability to result in a live birth, or a confinement proper. The delay in the renewal of ovulation, finally, is subject to random variation." We have so far considered the first of these random processes. In its application to the recorded data, it revealed the existence of certain infecund periods included in the recorded intervals. The third of the random processes suggested above means that these infecund periods may themselves be the result of a random process. Louis Henry has not indicated the nature of this random process. But the following may be postulated.

We may suppose, for instance, that each month after confinement, there is a certain probability that the ovulation may renew and that the actual delay in its renewal is the result of the operation of this probability. The recorded interval between two confinements may thus be regarded as consisting of three parts: (1) interval between confinement and renewal of ovulation, (2) interval between renewal of ovulation and conception, and (3) interval between conception and confinement, namely, the period of pregnancy. According to the hypothesis being suggested above, the first two of these intervals are the results of the operations of two independent probabilities, respectively, namely a probability of renewal of ovulation each month after confinement and a probability of conception each month after the renewal of ovulation. The third interval may be regarded as more or less constant and not subject to chance operation. Algebraically, we may state this as follows:

If x is the recorded interval,

$$x = x_1 + x_2 + c$$

where x_1 is the interval between confinement and renewal of ovulation, x_2 is the interval between renewal of ovulation and conception and c is the pregnancy period. Here x_1 is to be regarded the result of a probability p_1 of renewal of ovulation each month after confinement, and x_2 is to be regarded the result of a probability p_2 of conception each month after the renewal of ovulation. Here c is to be regarded a constant.

Means and variances of the intervals x_1 and x_2 are given, respectively, by

$$\text{Mean } (x_1) = (1\text{-}p_1)/p_1; \text{ Variance } (x_1) = (1\text{-}p_1)/p_1^2$$

$$\text{Mean } (x_2) = (1\text{-}p_2)/p_2; \text{ Variance } (x_2) = (1\text{-}p_2)/p_2^2.$$

The mean of the recorded interval is therefore given by

$$\text{Mean } (x) = (1\text{-}p_1)/p_1 + (1\text{-}p_2)/p_2 + c.$$

If the two probabilities, namely, of renewal of ovulation and of conception are regarded independent, the variance of the recorded interval x is given by

$$\text{Variance } (x) = (1\text{-}p_1)/p_1^2 + (1\text{-}p_2)/p_2^2.$$

These formulae for the mean and variance of the recorded intervals lead to the following relationship between the two:

Variance (x) cannot be less than (mean $- c$) (mean $- c + 2$)/2.

In Table 3, we give the minimum values of c which satisfy this relation between the variance and mean. It will be seen that these values of c are only a little smaller than the estimates of infecund periods given in Table 2 and that, in particular, the values of c are not close to 9 months which would be the normal pregnancy period. This means that the probability of the renewal of ovulation is zero not only during pregnancy but also for some time after confinement. If we regard 9 months to be the normal period of pregnancy, the difference between the values of c

TABLE 3

Family No.	C	$p = p_1 = p_2$	*Family No.*	C	$p = p_1 = p_2$
1	16.35	.5486	24	23.42	.2087
2	30.35	.5486	25	14.94	.2038
3	16.24	.4432	26	21.65	.2030
4	33.89	.4343	27	15.89	.1978
5	16.71	.4178	28	16.64	.1978
6	17.71	.4178	29	24.50	.1861
7	22.88	.4104	30	35.23	.1815
8	27.88	.4104	31	28.47	.1773
9	12.49	.3630	32	15.91	.1763
10	23.45	.3451	33	18.59	.1753
11	16.32	.3371	34	28.03	.1706
12	18.11	.3132	35	27.16	.1654
13	14.95	.2940	36	8.73	.1630
14	27.30	.2683	37	23.74	.1567
15	20.99	.2664	38	11.51	.1540
16	19.09	.2611	39	14.18	.1530
17	29.09	.2611	40	18.83	.1437
18	14.58	.2376	41	21.95	.1374
19	15.57	.2304	42	11.64	.1324
20	14.23	.2281	43	15.23	.1248
21	12.73	.2158	44	19.18	.1245
22	13.73	.2158	45	13.49	.1193
23	13.32	.2122	46	13.61	.1103

and 9 months gives us the estimates of this post-partem sterile period.

As mentioned above, the values of c given in Table 3 are the minimum values. They just satisfy the relation between the variance and the mean. That is to say, for these values of c the variance just equals (mean $-$ c) $\times$ (mean $-$ c $+$ 2) /2. These are also the values of c which make the two probabilities p_1 and p_2, namely, of renewal of ovulation and of conception equal. Such equal values of p_1 and p_2 corresponding to the minimum values of c are also shown in Table 3. The maximum values of c are those shown as infecund period in Table 2. For these values of c, the probability p_1 of renewal of the ovulation is 1; that is to say, we no more regard the renewal of ovulation, after a certain post-partem sterile period, a chance phenomenon but rather a certainty. Under those conditions, the values of the probabilities p_2, namely, of conception, are given by what are shown as fecundabilities in Table 2.

Probably the facts lie somewhere between these two extremes. The post-partem sterile period together with the pregnancy period lies somewhere between the minimum values of c given in Table 3 and the estimates of the infecund periods given in Table 2. The values of probabilities p_1 of renewal of ovulation lie between the values of p given in Table 3 and the value 1. The values of probabilities p_2 of conception lie somewhere between the values of p given in Table 3 and the values of fecundabilities given in Table 2.

In conclusion, we may note that the striking feature of the data given by Louis Henry is the rather small internal variances of intervals between confinements. These small variances can be explained only on the assumption of a considerable post-partem sterile period during which not only fecundability but even the probability of renewal of ovulation is zero.

THE SEX RATIO AT BIRTH OF THE KOREAN POPULATION*

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INTRODUCTION

IN NUMEROUS REPORTS ON THE SEX RATIO at birth of not only the human population but also many animals, it has generally been believed that the birth rate of males is, except for some rare species, about the same as that of females.

Ever since Graunt (1662) and Süssmilch (1741) reported that male births, compared with female, always show a numerical superiority, many workers have accepted their reports as quite reliable. As long as the mechanism of sex determination is explained by the action of X- and Y-chromosomes, the chances are 100:100 for both boys and girls. In practice, no matter what the theory, the higher rate is reportedly ascribed to male births.

Many differing opinions have been offered tentatively concerning reasons for the higher birth rate of males. Some of these are as follows:

1. Y-sperms are able to achieve fertilization more frequently than X sperms. This view was held in common by Schultz (1918), Hertwig (1927), and Ciocco (1938). Schultz observed that the sex ratios of stillbirths after fertilization of 3 months, 4 months, and 5 months were 123.7, 110.5, and 108.1, respectively. He furthermore claimed that the rate of stillbirths is 4 out of every 100 births, 8-10 months after fertilization; 9 out of 100, 4-9 months after fertilization; 14 out of 100, 3 months after fertilization. In his report on the sex ratios of stillborn or aborted children in several countries, Hertwig gave the following figures—128.3 in Germany, 142.2 in France, 131.1 in Italy, and 132.2 in Austria. Ciocco, in his sex-ratio study, reached similar results, thus endorsing the report of Schultz; that is, the longer the embryo remained in the uterus, the more the ratio decreased. This hypothesis, the present writers are led to believe, is more or less acceptable. It still lacks, however, some enforcement of the theory that Y-sperms have more chance to fertilize the eggs than X-sperms.

2. There is a commonly held view of long standing that Y-sperms are slightly lighter than X-sperms. However, this view is not acceptable because it has become clear that sperms do not approach eggs in the oviduct by swimming.

3. Hoelzel, Da Costa, and Carlson (1939) tried to solve the phenomenon (i.e., Y-sperms having more chance of

*Some references are incomplete because of the loss of many journals and reprints during the Korean War.

fertilization) with the hypothesis that in fertilization the equilibrium of the sexual hormones of the two sexes is maintained. According to Hoelzel *et al.*, X-sperms in the male organs are more likely to be destroyed when they are combined with the X-chromosomes from the maternal side because the function of the sexual hormones could not be kept well balanced under these conditions. In other words, X-sperms which include X-chromosomes like eggs are easily repulsed by eggs, whereas Y-sperms are easily attracted by eggs, thus enabling Y-sperms to be fertilized more frequently with eggs.

As enumerated above, each hypothesis may claim soundness for its own viewpoint; nevertheless, none of them is founded, so far, on sufficient experimental fact. Further studies in this field must be made to bring about a final solution. The present writers have simply emphasized the well-known fact that Y-sperms more frequently fertilize eggs than X-sperms.

The following report is a brief summary of research which the writers have undertaken on the sex ratio at birth of the Korean population, using material collected in recent years.* The writers hope that this report may cast light on establishing the actual situation in Korea in regard to the problem of the sex ratio at birth.

METHODS AND EXTENT OF THE INVESTIGATIONS

1. *The Investigation of* 1956

The investigation of 1956 covered 14,655 families in Seoul, 3,572 families in Cheju Island, and 280 families in Ulnung Island. These families were asked to give their sex and the number of births taking place among them from April 1, 1955 through March 31, 1956.

2. *The Investigation of* 1957

The investigation of 1957 covered 12,616 families in 27 towns or rural areas in Korea. The same method was used as for the year 1956, for the period from April 1, 1956 through March 31, 1957.

3. *The Investigation of* 1958

For this investigation 10,914 families in many parts of Korea were sampled. Information such as the number of births, sex, birth order, and age of mothers at birth was obtained. This time particular attention was given to eliminating bias—the informants, as they were students, were asked to report on families others than their own, such as those of their uncles, cousins, neighbors, etc.

RESULTS AND DISCUSSION

With the material aid obtained from the above investigations, the problem of the sex ratio of the Korean population can now be discussed.

1. *Historical Review.*

Ever since Graunt and Süssmilch estimated that more boys are born than girls, many workers have accepted this view. Lewis and Lewis (1906), Hartwig (1927), Russell (1936), and Ciocco (1938) made studies on the sex ratio at birth of the world population, and they all reported their findings. They all were of the opinion that 104-106 boys are born for each 100 girls.

Russell (1936) reported that the sex ratio at birth in Korea is 113.1, which indicates it to be one of the highest in

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the world. Many writers have followed Russell, expressing the view that the sex ratio at birth in Korea is one of the highest. Some other data, which have been collected through an official channel, indicate a still higher ratio than Russell's.

On the other hand, Matsuyama (1944) reported that the sex ratio at birth in Korea was the lowest: 100.7. He obtained his material from families of out-patients at the University Hospital. According to Matsuyama, previous statistical reports such as Russell's and his followers, which had described the Korean sex ratio at birth as one of the highest, were not supported by sound, unbiased investigation. Their observations, Matsuyama remarked, may have included enormous errors because of neglecting to consider the age-old attitude of the Korean family—that Koreans are better pleased to have boys born than girls. He asserted, therefore, that the previous data had erroneously shown a much higher ratio than actually existed.

With these two widely differing views in mind, the present writers wish to show their own findings. Table 1 on the sex ratio at birth is based on data collected recently during a three-year period.

TABLE 1

SEX RATIO AT BIRTH OF KOREAN POPULATION

Year Investigated	*No. of Births*		*Sex Ratio at Birth*
	Male	*Female*	
1956	916	807	113.51 ± 2.56
1957	1,041	913	114.02 ± 2.14
1958	24,273	21,091	115.09 ± 0.50
Average	26,230	22,811	114.99 ± 0.48

$X^2 = 0.12$, $DF = 2$, $P \div 0.95$.

Comparing the ratio in Table 1 with other countries, the writers can fairly assert that Koreans possess the highest sex ratio at birth in the world. In the present study possible errors which may have occurred in the investigation conducted through official channels, as Matsuyama pointed out, are eliminated because students participated directly in the investigation. Still the result favors Russell's findings. Furthermore we are led to believe that the method used by Matsuyama—collecting material from patients—is not sound and thus less reliable, for this study has discovered that the sex ratio is low when the parents are physically weak and high when they are healthy. Matsuyama's findings, therefore, came from an extremely uncommon situation. The present writers are certain that the sex ratio at birth of the Koreans still stands among the highest in the world population, as the average sex ratio of Koreans from 1956 to 1958 is 114.99, and the ratio is not significantly different for observation during a three-year period.

The following reasons are assumed to explain the high sex ratio at birth of the Koreans: (1) Still unknown factors accelerating the fertilization of Y-sperms with eggs may be more widely distributed among the Korean population. (2) Korean women may have better physical constitutions than those of other countries. (3) Lethal factors are only slightly distributed in Korea.

The present writers are not able to put forth with certainty any one of these factors above as an explanation. Further hereditary studies of the Korean population may throw light on this problem. The solution must be awaited.

2. *Sex Ratio at Birth* (classified by area)

Table 2 shows the number of newborn in these areas: Seoul, Cheju Island, Ulnung Island, and other rural areas in the Korean mainland.

Table 2 shows that birth rates are

TABLE 2

NUMBER OF NEWBORN AND BIRTH RATES

Areas Investigated	*Population Investigated*	*No. of Newborn*			*Birth Rate*
		Male	*Female*	*Total*	
Seoul	102,673	688	597	1,285	12.51 ± 1.09
Cheju Island	21,708	186	171	357	16.45 ± 3.44
Ulnung Island	1,563	42	39	81	51.82 ± 19.36
Rural areas in mainland	96,075	1,041	913	1,954	20.34 ± 1.75
Total	222,019	1,957	1,720	3,677	16.56 ± 1.08

lower in Seoul and Cheju Island than in the other rural areas. Using this table, the following sex ratio is established (Table 3).

TABLE 3

SEX RATIO AT BIRTH IN AREAS OF KOREA

Areas Investigated	*Sex Ratio at Birth*
Seoul	115.24 ± 2.99
Cheju Island	108.77 ± 4.97
Ulnung Island	107.69 ± 11.53
Rural areas in mainland	114.02 ± 2.14
Average	113.78 ± 1.76

$X^2 = 0.30$, $DF = 3$, $P \div 0.95$.

The average sex ratio in these areas is 113.78, and although each area does not show a statistically significant difference, it is clear that in Seoul and in the rural areas on the mainland the sex ratio at birth is higher than in the islands of Cheju and Ulnung.

Ciocco (1938) remarked in his report on the American sex ratio at birth, comparing American urban and rural areas, that there was no significant difference between the two regions, admitting the tendency for more boys to be born in urban areas than girls. Contrary to this finding, Düsing (1884) of Prussia, Lewis and Lewis (1906) of Scotland, and Russell (1936) of England were all of the opinion that the rate of male births is higher in rural areas than in urban. The present writers have found that in the urban area (Seoul) more boys were born than in the rural areas. In the islands the ratio is far lower, which may be explained in the following way: In the rural areas, when newborn children were dead, they were omitted from the register of births, although they should have been included for the present study, for the rural areas are composed of comparatively less-educated groups. And among the dead, newborn boys were probably more numerous than girls. Another assumption is that sex-linked lethal genes are perhaps more widely distributed in rural areas. If this assumption is reliable, the sex ratio of the newborn might be more or less decreased in the rural areas. But further analysis of these assumptions should be made in the future, and as one method of analysis the writers have tried to calculate both the rates of marriage and fertility.

3. *Sex Ratio at Birth By Different Occupational Groups of Fathers*

The sex ratio at birth has been examined according to the occupations of the fathers. For this purpose occupations are divided into four classes: mental, semi-mental (semi-physical), physical, and others.

As clearly observed in Table 4, the sex ratio is higher when fathers are engaged in physical work.

In Cheju Island (Kang and Cho, 1958), where the occupational grouping of fathers presents a specific aspect, no significant variation has come to light according to the occupational groups.

TABLE 4

SEX RATIO AT BIRTH BY DIFFERENT OCCUPATIONAL GROUPS OF FATHERS

Occupation	*Seoul*	*Cheju Island*	*Other Mainland Korean Areas*	*No. of Births Male*	*Female*	*Average Sex Ratio*
Mental work	104.28 ± 5.21	129.41 ± 18.21	126.77 ± 6.63	378	333	113.51 ± 3.99
Semi-mental work	122.34 ± 4.49	97.37 ± 11.39	102.16 ± 5.22	560	496	112.90 ± 3.26
Physical work	147.88 ± 9.17	109.01 ± 6.83	116.03 ± 3.04	899	762	117.97 ± 2.66
Others	84.38 ± 8.44	120.00 ± 33.40	85.71 ± 14.78	78	90	86.67 ± 7.17
Average	115.05 ± 2.99	108.77 ± 4.97	114.02 ± 2.14	1,915	1,681	113.92 ± 1.76

$X^2 = 3.67$, $DF = 3$, $P \div 0.30$.

The sex ratio at birth, however, seemed to be higher in the physical-occupation group.

Bernstein (1954) classified the occupations of parents into masculine and feminine (originally Terman's classification) and pointed out that the higher sex ratio results from the parents' employment in a masculine occupation. Her results are tabulated as follows:

TABLE 5

SEX RATIO AT BIRTH ACCORDING TO OCCUPATION OF PARENTS
(Bernstein, 1954)

	Sex Ratio at Birth	*Sex Ratio at Birth of 1st Born*
*I	140.0	144.3
II	107.3	111.1
III	105.6	115.9
IV	85.7	85.1
Average	109.0	112.3

*I Parents in masculine occupation.
II Fathers in masculine, mothers in feminine.
III Fathers in feminine, mothers in masculine.
IV Parents in feminine occupation.

Bernstein's results are founded on the belief that one's occupation is ordinarily chosen according to his character; that is, those who have a masculine character are employed in a masculine occupation; those with a feminine character in a feminine one. They are also based on the belief that Terman's adaptation test can appropriately be applied in his classifiication of occupation.

The present writers have found almost the same results as Bernstein. Parents whose occupations are physical (masculine in Bernstein's category) have delivered more boys than those in other occupations. The sex ratio at birth has been shown to be the lowest among parents occupied in mental work. Especially the column "Others" in Table 4, which includes artists, journalists, and clergy (occupations all under the feminine category in Bernstein's classification), shows the lowest sex ratio at birth except in Cheju Island.

4. *The Sex Ratio at Birth According to Father's Education*

In research done in 1958 the present writers examined the educational background of 10,914 families. Table 6 is based on these findings.

TABLE 6

SEX RATIO AT BIRTH ACCORDING TO FATHER'S EDUCATION

Father's Educational Level	*No. of Births Male*	*Female*	*Sex Ratio*
College graduate	5,280	4,616	114.4 ± 1.1
High-school graduate	9,121	7,951	114.7 ± 0.8
Elementary-school graduate	6,572	5,700	115.3 ± 1.0
No education	3,300	2,824	116.9 ± 1.4
Total	24,273	21,091	115.1 ± 0.5

$X^2 = 0.50$, $DF = 3$ $P > 0.90$.

Table 6 indicates that the more highly educated the fathers, the lower is the sex ratio at birth. The difference, however is slight and is not at a significant level. It is apparently correlated with "the sex ratio at birth and occupation," which has been studied above. It is also according to common sense that highly educated persons would be employed in mental work, and the less educated in physical occupations.

5. *Sex Ratio at Birth and Parents' Age*

Table 7 is based on the data from 1958 in which the age of parents from 10,792 families was known; it indicates the relation of the sex ratio at birth to the age of parents.

TABLE 7

SEX RATIO AT BIRTH AND PARENTS' AGE

	No. of Births Male	Female	*Sex Ratio at Birth*
•I	20,688	17,853	115.9 ± 0.5
II	1,439	1,289	111.6 ± 2.0
III	1,911	1,757	108.8 ± 1.7
Total	24,038	20,899	115.0 ± 0.5

$X^2 = 4.00$, $DF = 2$, $P > 0.10$.

•I Fathers older than mothers.
II Ages of fathers same as mothers.
III Fathers younger than mothers.

When fathers are older than mothers, the sex ratio is extremely high; when fathers are younger, the ratio is low. And the ratio is significantly different for parental-age relationships.

Many studies have been made on the relation of the sex ratio at birth to the parents' age, and yet none seem satisfactory as their results are so diverse.

Hofacker (1827) and Sadler (1830) said that when fathers are older than mothers the sex ratio at birth is much higher than in the opposite situation. Ciocco (1938) reported that with parents the same age the sex ratio at birth is higher than when they are of different ages. The same view had been expressed by Stieda in 1875.

It is still commonly accepted that when fathers are younger than mothers the sex ratio at birth is low. The present writers could confirm this view throughout their study of various reports and observations. When the age of parents differs, the sex ratio at birth also varies, but the reason for this variation has not been clarified as yet. It remains for future research to determine.

6. *The Sex Ratio at Birth and Parents' Health*

Table 8 shows the relation of the ratio at birth to the parents' health.

TABLE 8

SEX RATIO AT BIRTH AND PARENTS' HEALTH

	No of Births Male	Female	*Sex Ratio at Birth*
•I	7,902	6,889	114.7 ± 0.9
II	3,272	2,907	112.6 ± 1.3
III	11,493	9,824	117.0 ± 0.7
IV	1,606	1,471	109.2 ± 1.9
Total	24,273	21,091	115.1 ± 0.5

$X^2 = 4.36$, $DF = 3$, $P > 0.10$.

•I Fathers healthier than mothers.
II Fathers less healthy than mothers.
III Both with healthy constitutions.
IV Both with weak constitutions.

Table 8 indicates a higher sex ratio, showing significantly different levels with both parents in good health than when both are physically weak. This result leads to the establishment of the following hypothesis: When the health of the parents is good, there is a greater possibility for sound growth of the embryo. The finding, known from previous studies, that there is a higher birth rate for males in stillbirths and abortions, is evident verification that more boys are apt to be born when the parents are in sound health. If the parents are weak, the embryo also may become weak and consequently a higher death rate of embryos may follow.

7 *Birth Order*

Many research workers have observed that the sex ratio at birth varies with birth order. The present writers also have examined the relation of the sex ratio of the newborn to birth order. The following results were obtained:

TABLE 9

SEX RATIO AT BIRTH ACCORDING TO BIRTH ORDER

Birth Order	*No. of Births*		*Sex Ratio at Birth*
	Male	*Female*	
1	5,745	4,621	124.3 ± 1.1
2	5,310	4,501	118.0 ± 1.1
3	4,479	3,945	113.5 ± 1.1
4	3,040	2,701	112.6 ± 1.4
5	2,116	1,976	107.1 ± 1.6
6	2,378	2,207	107.7 ± 1.5
7 & more	1,205	1,140	105.7 ± 2.1
Total	24,273	21,091	115.1 ± 0.5

Studies have been made on the relation between the sex ratio at birth and birth order by Lewis and Lewis (1906), Ciocco (1938), Lawrence (1951), and MacMahon and Pugh (1953); they have all asserted that the sex ratio of the first-born is comparatively higher. Table 10 was made by Ciocco in his study of the American population.

TABLE 10

BIRTH ORDER AND SEX RATIO AT BIRTH
(Ciocco, 1938)

Birth Order	*Sex Ratio*
I	106.3
II	106.0
III	105.9
IV	105.3
V & more	105.1

King (1918) conducted experiments with albino rats, observing the sex ratio at birth in relation to birth order, and established the ratio of the first-born to be 112.0 and that of the fourth-born to be 103.1. The findings of the present writers also disclose that the sex ratio at birth decreases as mothers bear more children. The reason for this decrease has not yet been discovered, although many writers have tentatively suggested that the physical constitutions of mothers become weakened in proportion to the extent of their childbearing.

8. *The Sex Ratio and Mother's Age*

Following the research of Hofacker (1827) and Sadler (1830), many scholars such as Russell (1936), Martin (1948), Jalavisto (1952), Bernstein (1953), Novitski (1953) and Novitski and Kimball (1958) conducted studies on the problem of the sex ratio at birth and age of mother. Table 11 is based on the findings of the present writers.

TABLE 11

SEX RATIO AND MOTHER'S AGE

Mother's Age	*No. of Births*		*Sex Ratio at Birth*
	Male	Female	
20 & less	1,752	1,447	112.1 ± 1.9
21-25	7,683	6,460	118.9 ± 0.9
26-30	7,308	6,361	114.9 ± 0.9
31-35	4,598	4,146	110.9 ± 1.1
36-40	2,290	2,087	109.7 ± 1.6
41-45	588	539	109.1 ± 3.1
46 & more	54	51	105.9 ±10.1
Total	24,273	21,091	115.1 ± 0.5

$X^2 = 12.31$, $DF = 6$, $P > 0.05$.

The differential in Table 11 is significant. It indicates that the sex ratio at birth decreases as the age of mother increases.

Parkes (1926) pointed out that as mothers become older the sex ratio gradually decreases. Ciocco (1938), however, reported, after careful observations undertaken four times from 1917 through 1934 on the American population, that it was almost fruitless to try to find a certain trend in the sex ratio related to the mother's age, even though he isolated the differential in the sex ratio: 105.8 in mothers under 30 years old, 105.3 in mothers over 30. On the other hand, Novitski (1953), Jalavisto (1952), Novitski and Kimball (1958) reported that the sex ratio at birth was affected far less by mother's age than by father's age.

Novitski (1953) reported that the sex ratio at birth presented a simple linear regression according to the increase of father's age. However, Novitski—later in collaboration with Kimball (1958)—studying the American population, modified his former view in regard to the sex ratio and birth order and parents' age. He remarked that the secondary sex ratio is more affected by father's age than mother's and that the variation of the sex ratio according to parents' age presented a somewhat curved line rather than a simple one although it was impossible to make an equation to fit this relationship.

Since the present writers are not provided with data to explain the variation of the sex ratio according to age of father, it is impossible to insert our own viewpoint at this time. That mother's age brings about a variation in the secondary sex ratio has already been seen. The reason for this is very simple: the increase in age of mother causes general weakening in her constitution and deterioration of the quality of the eggs in particular. A similar observation can be made for the paternal side: as the age of father increases, the sperms deteriorate and fertilization is not accomplished so smoothly as before—thus the sex ratio might vary. If the gravity of the damage at birth owing to increased age on both paternal and maternal sides were properly evaluated, the relation of the sex ratio at birth varying with the age of father and mother would become clearly known. This problem still remains to be solved by future research.

SUMMARY

The writers have obtained some data on the sex ratio at birth of the Korean population to use as material for studies in population genetics.

1. The sex ratio at birth in Korea reveals the highest ratio among world populations as Russell (1936) had measured it. The ratio is 114.99.

2. The ratio is shown to be higher in Seoul and in other parts of the Korean mainland (114-115) than in the two islands, Cheju and Ulnung (107-109).

3. The ratios of groups engaged in mental and semi-physical occupations are shown to be lower than those of groups engaged in physical labor.

4. The ratios tend to decrease as fathers become more educated. But these ratios do not differ at significant levels.

5. When fathers are older than mothers, the ratio is high. But when the converse in regard to age is true, the ratio is lower.

6. When fathers and mothers both are healthy, the ratio is shown to be higher than when both have weak physical constitutions.

7. As a number of writers have already done, the present writers point out that the sex ratio is higher among the first-born and lower in the subsequent births of Korean children.

8. The ratio is higher when the mothers are younger, but as the age of mother increases, the ratio decreases inversely.

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Book Reviews

HEREDITY OF THE BLOOD GROUPS: Alexander S. Wiener and Irving B. Wexler. Grune & Stratton, New York, 1958, x + 150 pp., 51 tables, 4 figs.

The authors have attempted to condense in these 150 pages ". . . in a unified manner, the facts known about the heredity of the human blood groups." The general layout of this monograph conforms with that of an earlier review on the subject by Race and Sanger of which the third edition has recently been out. It, however, differs from its predecessor in one essential respect. We are told in the preface that ". . . in all cases, heredity is by multiple allelic genes, not only in the A-B-O system, but also in the Rh-Hr and M-N-S system . . ." and ". . . at the very onset, the important distinction between a blood factor and an agglutinogen is pointed out . . . to explain the serology, genetics and nomenclature of the A-B-O, Rh-Hr, M-N-S and other blood group systems." Parenthetically, Race and Sanger are the chief protagonists of another theory of closely linked loci for the Rh blood groups and a different system of nomenclature.

The subject matter is divided in 12 chapters of which 9 are concerned with the heredity of blood group systems and one each with introduction, medicolegal applications and anthropological studies. The shortest chapter, IX, on "The Kidd Blood Group" consists of 39 lines in contrast to chapter V on ::The Rh-Hr System" which is covered in 43 pages. There are 264 references (excluding No. 234, included also as No. 222) given at the end of the monograph and this corresponds to the same number of references for one chapter on "The Rh Blood Groups" by Race and Sanger. We could not, however, complain of an inadequate treatment of any part of the subject, as we are earlier told that ". . . an attempt has been made to include in this monograph only those reports which appear to be reliable." There is at least one exception to this. The authors have offered a hypothesis (presumably a new one) of three allelic genes to explain the Lewis saliva groups and a detailed discussion on it. They have, however not quoted an important paper by Grubb who had considered this very hypothesis earlier and had discarded it on the basis of his extensive observations reported in that paper. The authors have quoted some other papers by Grubb.

The latest position on the heredity of Rh-Hr types is this: "With the lack of evidence for crossing-over between the postulated gene pairs *D-d, C-c, E-e,* and *F-f,* Race has invoked the concept of 'complete' linkage. This latest alteration in the theory makes quite meaningless the concept of linear arrangement, since operationally, the linked gene theory thus becomes identical with the Wiener's theory of multiple alleles, . . ." (p. 100).

The position on Rh-Hr nomenclature has been stated thus: ". . . the recommendation that the Rh-Hr nomenclature be used exclusive for medicolegal reports . . ." may now be extended ". . . in clinical medicine and anthropology." The authors further point out that "Confusion will remain until editors of

scientific journals require that all articles dealing with Rh-Hr types conform with this recommendation, as has been done in the case of the analogous recommedation made in a report[234] published in 1937, regarding the nomenclature of the A-B-O blood group." (pp. 128-129).

Some references are not quoted quite correctly, e.g. Lawler[174] (p. 95) and no reference for R. Sanger (p. 111). Some statements are not quite up to date, e.g. "Such reagents, (anti-O) which are now commonly designated as anti-H. . . ." (p. 30).

The monograph stands in sharp contrast to the masterly review of "Blood Groups and Transfusion" by the senior author, which was first published in 1935 and which went into three editions and several printings. The last edition of that book was prepared in 1943, the year in which Karl Landsteiner died and to whom the present monograph has been dedicated with a frontispiece. The monograph gives an incomplete coverage of the field, highlighting mainly the work and the views of the senior author. If one of the purposes of writing this monograph was to ensure that blood group workers, particularly outside of the U.S.A. should pay more attention to the views of the authors, one regrets to say that this also is not done in a convincing manner.

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Hämophilie B. Genetische, klinische und gerinnungsphysiologische Aspekte — Untersuchungen an einem weitverbreiteten Bluterstamm (Hemophilia B. Genetics, Clinical Aspects, and Coagulation Physiology—Examinations of a Widespread Hemophilia Pedigree): J. K. Moor-Jankowski, H. J. Huser, S. Rosin, G. Truog, M. Schneeberger, and M. Geiger. *Separatum* "Acta Genetica et Statistica Medica" 7, 4 (1957), 8, 1 (1958). S. Karger, Basel & New York, 1958. 234 pp., 52 tables, and 7 figures, sfr. 34.

This monograph summarizes the results of an extremely thorough and careful re-examination of the well-known hemophilic family of Tenna. Here, 3072 descendants and relatives by marriage from the progeny of a married couple which lived in the middle of the 17th century have been examined, 56 of which turned out to be hemophilics. Out of this number 13 were alive at the time of the examination; 10 were examined, using modern techniques of coagulation physiology, and these showed a factor IX deficiency (PTC). In the first part, which is by far the most extensive one of the whole work, the collection of the material and the demography of the trait are described. In addition, it contains a description of the single members of the Tenna family as well as a discussion of the results in coagulation physiology and population genetics which are discussed in a more detailed way in the two papers following. A very good survey is given on the latest genetic knowledge of coagulation deficiency.

These are the chief conclusions of the work:

1. The examination of blood coagulations of 10 living bleeders showed a remarkable resemblance in the extent of the factor IX deficiency. (Blood level 2.5–6 per cent; normal: 60–180 per cent). The clinical symptoms, however, were of different grade between the bleeders and generally decreased during life.

2. The examination of 11 female heterozygotes (carriers) showed entirely normal factor IX levels, and after a thorough consideration of all statements an increased tendency toward hemorrhage could also be excluded. This result is contrary to what we know about quite a number of families showing a factor VIII deficiency (hemophilia A).
3. As for the hemophilics themselves, they are quite obviously at a selective disadvantage compared with a normal population living under equal conditions. Many of them died early, and on the whole their reproductive performance was only about two-thirds that of the normal. The fact that, in spite of this, the gene was able to spread so extensively can be explained in this family by an increased propagation of the female heterozygotes, that is, the carriers. The authors deduce from it that with hemophilia in general the selective disadvantage of the patients could possibly be compensated for by a selective advantage of the heterozygotes and that the assumption which was valid since Haldane (1935), who concluded that this compensation would result from new mutations, has proven to be wrong. Nevertheless, this conclusion cannot be based on a single pedigree. The mere fact that hemophilia did not die out in the course of three centuries is evidence enough that a compensation has really taken place and that this compensation was practically only made possible by an increased fertility of the carriers. This means that the pedigree differs considerably in size and consequently in the fertility of the carriers from what we usually find in hemophilia. The pedigree has been selected for high fertility (by chance); hence general conclusions cannot be drawn. The hypothesis of the authors ought to be re-examined with some unselected material (all hemophilic families of the type B in a special area). This objection does not affect the high value of this work which, besides the problems mentioned above, gives evidence about many other problems some of which go beyond the medical sphere.

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THE CHEMICAL BASIS OF DEVELOPMENT: W. D. McElroy and Bentley Glass, Eds. Johns Hopkins Press, Baltimore, 1958, 960 pp., $15.00.

The volume, comprising the proceedings of the 1958 McCollum-Pratt Institute Symposium, represents an impressive collection of thought-provoking papers and discussions spanning the area of developmental biology.

To the "medical geneticist" certain papers are of immediately apparent interest. Markert, discussing genic control of development, proposes that differential gene activation and variation in genic stability play a major role in the differentiative process. Hughes, reporting on his studies with tritiated thymidine, presents his views on chromosome replication and cell proliferation, while Swift discusses possible mechanisms of nucleo-cytoplasmic interactions, as indicated by his electron-microscope studies of RNA localizations. Sussman analyzes slime mold aggregation, emphasizing the role of genetic factors in this process. Nace and Clarke, Ebert, and Billingham present work on immunochemical differentiation, and Hadorn reviews his classical studies on development genetics of *Drosophila*.

Discussing neoplastic development, Foulds presents an outstanding analysis of the sequence of events leading to neoplasia. He likens the initiation and promotion phases of tumorigenesis to embryonic determination and the subsequent realization of embryonic capacities. Originating in some or any cell capable of propagation, the end product of the neoplastic process is considered to be hereditary, irreversible and qualitatively distinct.

It is time to realize, however—and this volume helps to make one realize—that the geneticist cannot rely for information and stimulation only on those papers dealing with "genetic" topics. Work on enzyme induction in dissociated embryonic cells, on feedback mechanisms, on liver regeneration, on intercellular materials: here is crucially important literature for the geneticist of today.

It is interesting to notice that the expansion of developmental biology has not been uni-directional. While refined techniques of chemical analysis and microscopy have increased our awareness of sub-cellular chemical and structural entities, there is at the same time an increasing emphasis on supra-cellular phenomena such as cell aggregations, intercellular materials and cell-to-cell communication.

Paul Weiss, in summation, states: "The general excellence of the meetings defies any attempt to squeeze an evaluation into such a short period." Suffice it to say that the published volume of these meetings is a noteworthy addition to the literature of developmental biology.

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THIRTY YEARS OF RESEARCH IN HUMAN FERTILITY: RETROSPECT AND PROSPECT (Papers Presented at the 1958 Annual Conference of the Milbank Memorial Fund, Held October 22-23, 1958, at the New York Academy of Medicine, Part II). Milbank Memorial Fund, New York, 1959. 158 pp. $1.00.

Demographers look forward to the publication of the proceedings of the annual conferences of the Milbank Memorial Fund, confidently expecting an up-to-the-minute, if selective, report on current research in one or another of the major fields of population research. The 1958 conference was somewhat distinctive in that time was taken for a few backward glances at developments during the last few decades in an area where the Fund has concentrated its efforts—human fertility.

The "retrospect" consists mainly of Hajnal's urbane and illuminating account of changing views on methods of measuring fertility and reproduction and Ryder's sophisticated re-study of fertility trends in this country, making use of the latest developments in cohort analysis. Current status and "prospects" are covered by reviews of needed improvements in official data (Grabill and Schacter) and of current research on physiological control of fertility (Nelson), along with reports from the project on "Growth of American Families" (Freedman, Campbell) and the "Study of the Future Fertility of Two-Child Families" (Potter, Westoff, Sagi). The reader who wishes to get abreast of current thinking and research in the field covered by the conference will find the volume useful. Anyone who may be unaware of the leading role played by the Milbank Memorial Fund in this field should peruse Boudreau's informal account of the work

of its Division of Research, which concludes the volume.

Since most of the papers are in the nature of progress reports or summaries of studies, it would not be appropriate to scrutinize them in detail. I would like to record an opinion on just one point. It seems to me that the increasing differentiation and specialization of approaches to the study of human fertility require a periodic assessment of the overall strategy of research on the subject. It is clear that technical innovations in the social sciences—particularly the depth interview and the opinion survey—are having a major influence in determining methods of inquiry. It is not usually acknowledged, however, that the new techniques of investigation have led to a radical restatement of the substantive problem. In the kind of research reported most fully here, we are no longer interested in the *fertility of populations* and determinants thereof but in the fertility *behavior of couples.* While the Indianapolis Study was initiated on the supposition that its results would clarify traditional problems of differentials and trends in fertility, the recent studies seem frankly preoccupied with micro-demographic and social-psychological questions for their own sake. Granted the intrinsic interest of these inquiries, what are we to assume about their relation to the urgent matter of understanding the tides of change in fertility levels, the pronounced disparities in effective fertility among nations and broad culture complexes, and the impact of implicit or explicit population policies on the evolution of fertility patterns? To put the matter bluntly and no doubt unfairly, what has been or can be discovered from the intensive interrogation of couples about their desires, values, attitudes, and personal orientations that will explain the "baby boom"?

Much as one wishes to see the approach pioneered by the Milbank group and associates exploited for all it is worth, it cannot be accepted as axiomatic that the direction they are taking leads to the greatest payoff. There is room for the suspicion that fundamental determinants of the fertility of populations can be disclosed only by imaginative and meticulous inquiry at the macro-demographic level.

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LA POPULATION DE CRULAI, PAROISSE NORMANDE — ÉTUDE HISTORIQUE: Étienne Gautier and Louis Henry. Institut national d'études demographiques, "Travaux et documents," No. 33, Paris, 1958. 272 pp.

Demography studies aggregates of human individuals who are not unrelated to each other. True, the actuarial parentage of this science, and limitations of available statistics, have often made it seem so. But, already in the eighteenth century, some students of population made use of ratios of recorded births to recorded marriages as significant measures of a vital process. It is Henry's great merit to have re-focused the attention of demographers on the process of family formation as the major point of origin of demographic phenomena.

Henry's first great venture in this direction was the development of an efficient technique of diagnosing the fertility trend of a disturbed period, e.g., a post-war baby boom (L. Henry, "Fécondité des Mariages—Nouvelle Méthode

de Mésure," Paris, 1953). The cornerstone of that method is the trend in rates at which families of each given size become families of the next larger size, as a result of births. To be perfect, the method would require current data on intervals between births of successive orders. Such data are not commonly found and had to be hypothesized—a technical flaw of the method, though practically not of much consequence.

No doubt it was the search for data on birth intervals that led Henry into the field of historical demography, in which he and his associates have already made some remarkable discoveries.

In recent centuries parish registers of baptisms, marriages, and funerals were systematically kept in France, other parts of Europe, and also French Canada. Many records have been preserved and, when suitably combined, provide rich material for the study of the process of family formation in populations where modern practices of birth control were unknown. In the French literature, such populations are referred to as "pre-Malthusian" populations.

The practical procedure for dealing with such material has been outlined in a manual by Fleury and Henry, "Des Régistres Paroissiaux à L'Histoire de la Population" (Paris, 1956). One major application of such procedures was J. Henripin's "La Population Canadienne au Début du XVIII^{e} Siècle" (Paris, 1956); another was Henry's "Anciennes Familles Genevoises, Étude Démographique" (Paris, 1956); the present study of the Norman parish of Crulai is the third major opus of this genre.

These studies are no mere isolated curiosities. They permit comparison of findings, among themselves, and with various other current studies. A body of knowledge concerning processes of family formation in "pre-Malthusian" populations is thus being progressively solidified. The special feature of the Crulai study is that this is the first consistent and scientifically impeccable analysis of the same process in a rural community that has been remarkably stable.

The constancy in the size of Crulai is noteworthy. From about 1650 to 1850 it had almost invariably the same population. The number of land holdings, furthermore, has hardly changed to the present day. Up to the French Revolution, this stability resulted from a birth rate averaging 36, a death rate averaging 31, and a net emigration of 5 per 1,000 inhabitants per year.

Migration was not negligible. There were numerous marriages of persons originating in Crulai and other, nearby, parishes. Foster-children were brought to Crulai from Paris. Natives of Crulai emigrated, probably often to Paris. The net outward balance, though steady, was small.

Mortality fluctuated; its high average level was inevitable. Appreciable changes in economic and social conditions did not seem to occur. Stability, under the conditions, depended on maintenance of a birth rate not differing much from the one actually observed. Part of the mechanism by which this birth rate was maintained is social, and part of it is physiological.

An evidently social part of the mechanism was the successful enforcement of extra-marital taboos. In fact, pre-marital conceptions and illegitimate births were exceedingly rare. Marriages were postponed to the average ages of 27 for men and 24 for women, very much as at present. The remainder of the mechanism operated within marriages. Was this mechanism deterministic? Or is there any evidence of human free will?

A striking observation, almost invariably made in the "pre-Malthusian" populations, is found once more. Irrespective of age at marriage, married women of given ages have equal average fertility at these ages. The finding, once again, tends toward a presumption that fertility within marriage is physiologically determined. Henry emphasizes the finding, without giving it an explicit interpretation.

Another observation, made for the first time in Crulai, is a continuous increase of birth intervals with successive orders of birth. The finding is statistically significant, and Henry goes to much length to show that it is consistent with the hypothesis of a strictly physiological cause. Part of the argument hinges on observed, much shorter birth intervals on the occasion of an infant death. Continued nursing of surviving infants, then, may result in varying delays in the renewed onset of the menses. As the analysis of variance shows, these delays vary with successive birth orders (possibly as a function of age) as well as among individual women.

Another observation, on which Henry offers no comment, is the unusually long average interval preceding the last birth in a family. Here, the reader suspects an action of the human will. Thus, frequent attempts, however unsuccessful in many cases, not to have any more children, or not to have them soon again, may have produced such a result in the aggregate. This presumption, if valid, may also cast some further reflections on the increasing birth intervals noted above, on their variations among individual women, and on the short intervals following an infant death.

Henry's interpretations are partly obscured by terms such as "sterility," "fecundability," and "aptitude to procreate," used without a clear indication as to whether they are intended to define purely physiological conditions, or conditions in which deliberate human action, disposition, or willingness, play their part. Henry's analysis of the data is as sharp as is his restraint from explicit comments not necessarily supported by the facts. And perhaps he is right. There are gradations and mutual interferences of human ability and the human will. In the last resort, married couples are unable to do what they do not want to do.

But this is a burning question. By the records of "pre-Malthusian" Canada, marital fertility in contemporary populations having the "high" birth rates of 45 per 1,000 is low. Does a birth rate of "only" 45, despite early marriage, reflect sheer unrestrained capacity? If not, what is the nature and extent of the restraint? An answer to this and related questions can have far-reaching consequences.

Henry and his associates determinedly do not stray beyond the facts. Their historic studies, carried out with masterful skill, are highly illuminating. Findings of this type cannot be obtained from any available contemporary statistics. The historic studies, therefore, should be multiplied until responsible answers emerge to the crucial problems posed by the unknown relative roles of ability and dispositions in human fertility.

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Periodical Reviews

GENETICS

Observations of Kuru: I. A possible genetic basis. J. H. Bennett, F. A. Rhodes and H. N. Robson, *Australasian Annals of Medicine,* **7** (1958), pp. 269-275.

The authors propose a tentative genetic explanation for the neurological disease "kuru," which occurs at a high frequency among the Fore tribe of the Eastern Highlands of New Guinea. This fatal disease, which has only been known for a few years, has an incidence as high as 10 per cent in some areas. The occurrence of the disease is compatible with a hypothesis of a single autosomal gene "*K*" which is dominant in females and recessive in males. Females that are *KK* have an early onset of the disease, while *Kk* females are affected later in life. *KK* males have an early age of onset, but *Kk* males are clinically normal. Evidence for this hypothesis comes from the observations that male victims and young female victims are born to females with the disease; the incidence of the disease is similar in males and young female victims; and among adults, the incidence is much higher in females.

The high incidence of this disease among these people represents a remarkable situation. The selective disadvantage of the *K* gene, because of death due to kuru, must be compensated for by some other force maintaining the gene at such a high frequency in the population. The discovery of this force presents a challenge. Perhaps it takes the form of some selective advantage of the heterozygote, principally the male, in the particular environment occupied by the members of the population.

A case of human intersexuality having a possible XXY sex-determining mechanism. P. A. Jacobs and J. A. Strong, *Nature,* **183** (1959), pp. 302-303.

Cytological studies were carried out on an individual showing intersexual characteristics. The individual was male in appearance but was characterized by gonadal dysgenesis, gynecomastia, small testes, poor facial hair growth, and a high-pitched voice.

Smears of the buccal mucosa and blood showed nuclear sex chromatin that was typically "female." The chromosome number in the cells obtained by sternal marrow puncture was unquestionably 47. An X and Y chromosome were identified in addition to another chromosome having all the characteristics of an X chromosome. It is thus highly probable that the individual has an XXY sex chromosome complement. This could have arisen from non-disjunction of the sex chromosomes in the formation of the egg or sperm cell giving rise to the individual.

This observation is of basic genetic interest since if all XXY individuals are intersexes, then it would suggest that genes for "maleness' in man are associated with the Y chromosome because of the masculinizing effect of this chromosome. This differs from the well-studied situation in *Drosophila melanogaster,* where it has been shown that the Y chromosome lacks genes for the determination of sex. In this organism the genes for femaleness are largely on the X chromosome, and the genes for maleness are, purportedly, largely on the autosomes.

A follow-up study of hereditary chronic nephritis. G. T. Perkoff, C. A. Nugent, D. A. Dolowitz, F. E. Stephens, W. H. Carnes, and F. H. Tyler, *A. M. A. Archives of Internal Medicine,* **102** (1958), pp. 733-746.

In 1951 the authors presented the results of a study carried out on a large kindred exhibiting a hereditary form of a renal disease associated with nerve deafness. It was proposed that the distribution of affected individuals in the kindred is best explained by the segregation of a partially sex-linked dominant gene which shows reduced penetrance in females and variable expressivity in both sexes. The conclusion that the responsible gene is located on the homologous portions of the X and Y chromosomes came from the observation that in most branches of the kindred the trait appeared to behave as a typical sex-linked dominant trait, but in a few cases there were suggestions that crossing over had occurred between the X and Y chromosomes.

Since the publication of the 1951 paper, the authenticity of cases of partial sex-linkage in man has been questioned (Morton, N. E., *Am. J. Human Genetics,* 9 (1957), pp. 55-75.). For this kindred the purported crossovers were given another explanation, i.e., the trait is due to a sex-linked dominant gene and the normal daughters of affected males are asymptomatic carriers of the gene, as found elsewhere in the kindred, and the affected sons of affected males represent sporadic cases of nephritis of different etiological origin.

Following a six-year interval, the kindred was given a follow-up study. The authors conclude that the data still support the concept of partial sex-linkage. Although nothing conclusive can be said about the supposed female crossovers, it is noted that two males with nephritis, ages 12 and 20, were born to a man with nephritis and nerve deafness who received the gene from his mother. Both of the males are now beginning to show early signs of nerve deafness. This argues against the conclusion that these males represent sporadic cases of nephritis. It suggests, on the contrary, that the same gene causing the syndrome is present in father and sons. Further information on this problem might become available when the two males in question marry and have children. If the gene is located on the Y chromosome in these two individuals, then they should tend to pass the gene to their sons.

Human chromosome complements in normal somatic cells in culture. E. H. Y. Chu and N. H. Giles. *The American Journal of Human Genetics,* 11 (1959), pp. 63-79.

In a very careful and detailed study of the morphological aspects of chromosomes in somatic cells in tissue cultures derived from 34 different individuals, the authors conclude that each chromosome pair has characteristics that enable it to be identified. Distinguishing features are length, position of centromere, and presence or absence of satellites. The pairs of chromosomes were placed in 7 subgroups and each individual pair was given a number.

The X chromosome is 4 to 5 times longer than the Y chromosome. Statistical analyses showed that there is no significant difference in any measurable characteristic among X chromosomes, among Y chromosomes or among any of the homologous autosomes derived from cells of the same or different individuals.

Chromosome number determinations support the conclusion expressed by other workers that the diploid chromosome number in man, regardless of race, sex, age, or tissue, is 46.

ABO blood groups and sex ratios at birth. T. M. Allan, *British Medical Journal,* **5121** (1959), pp. 553-554.

Over the years inconclusive data have been published on the possible relationship between the ABO blood groups and the sex ratio at birth. In order to explore this question more fully, the author published blood-group data, including series of his own, on newborn babies and their parents. The measurement determined, known as the sex ratio, was the number of male births divided by the number of female births (M/F = Sex Ratio). Several important findings were noted. Among whites, the sex ratio of babies born to AB mothers is significantly higher than the sex ratio of babies born to O, A, and B mothers combined (1.26 vs. 1.08). The sex ratio of O babies born to O mothers is significantly higher than that of A babies born to A mothers (1.11 vs. 1.02), and lastly, the sex ratio among O babies is significantly higher than the sex ratio among A babies (1.11 vs. 1.03).

If the trends shown here can be supported in future studies, then these results emphasize again the selective value of blood groups. It is known that the sex ratio at conception is much higher than that at birth. Any factor increasing the probability of the survival of the fetus would tend to raise the sex ratio. It would seem that such factors may be the possession of blood group O by the fetus or heterosis in the mother caused by the heterozygosity of the genes for antigen A and B.

The problem of unilateral amblyopia. R. B. W. Cole, *British Medical Journal,* **5116** (1959), pp. 202-206.

The author states that it is surprising that unilateral amblyopia has not received from geneticists the attention which has been devoted to other eye conditions. A routine eye examination of 10,000 consecutive men, women, and children in England disclosed 5.27 per cent with this disorder. A condition is classified as unilateral amblyopia if one eye has reduced visual acuity, in the absence of any pathology, while the other has normal vision. The condition is known commonly as "lazy eye."

Family histories obtained by the author showed that there is a strong element of heredity in this condition. Since it has a relatively high frequency in the general population, the author stresses that efforts should be made to determine its mode of inheritance.

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POPULATION

Concerning equilibrium in human population. Richard L. Meier. *Social Problems* **6,** 2 (Fall 1958), 163-175.

Although worldwide adoption of birth control in one form or another seems necessary for a solution of the problem of population growth, it is sometimes overlooked that it would not be sufficient. Universal voluntary choice of the fertility level now exhibited by some of the most advanced countries would mean a growth rate very like that of the present. Assuming that the ability of the world to support people, however

great it may be, is not infinite, ways must ultimately be found of motivating substantial numbers of persons who have the means of limiting their fertility actually to do so.

In this article it is proposed that the solution may lie in the development of socially acceptable life styles that favor infertility. If family size were to be about what it now is in America, approximately one-third of all women would have to be drawn into occupational roles that would be satisfying and at the same time would discourage fertility. Occupations requiring geographical mobility and inconvenient time commitments, now largely limited to males, seem the most promising.

To complement the occupational structure that would favor low fertility, the author indicates that it would probably be necessary to create primary groupings for the infertile if their lives are to be satisfactory. Modifications of the companionate marriage and of the extended family system offer possibilities. Further questions discussed include the genetic effect of a tendency to select for infertility some of the presumably most competent individuals and the difficulties posed by nationalistic policies in a politically fragmented world.

Though the problems outlined in the article have been recognized before, it seems to the reviewer that they are worthy of more attention than they have received. The author has performed a valuable service in formulating them for consideration.

Differential fecundity and effectiveness of contraception. Christopher Tietze. *Eugenics Review* **50,** 4 (January 1959), 231-237.

To illustrate the time patterns according to which pregnancies will occur under specified assumptions as to fecundity and the use of contraception, the author considers a hypothetical population of couples some of whom are highly fecund, some moderately fecund, and some sub-fecund. Later in the analysis, a proportion of sterile couples is added. The levels of fecundity and the division of the population among the several categories are so chosen that the pregnancies that would result after the discontinuance of fully effective contraception are distributed over time in approximately the pattern exhibited in two earlier studies of real data. As the more fecund couples are eliminated from risk of pregnancy by the actual achievement of conception, the chance of conception among the remaining couples declines steadily and rapidly.

If it is assumed that the hypothetical population employs contraception that produces a 90 per cent reduction in the probability of conception for each couple, the total number of pregnancies experienced by the population over a two-year period is about 47 per cent below the number when no contraception is used. Contraception that is 99 per cent effective for individual couples reduces the number of pregnancies in two years for the entire group by about 92 per cent.

A complication in the study of contraceptive effectiveness is the period of post-partum sterility. Since the distribution of the length of this period is not fully known, it is often not clear in the case of contraception used within a few months after the termination of a pregnancy whether temporary sterility or the contraception is to be credited for any reduction in the level of fertility. On the other hand, as the analysis of the hypo-

thetical population showed, once fecundity is reestablished, the probability of conception for a group of couples declines from month to month, which further confuses efforts to obtain measures of contraception effectiveness. To help minimize the distortion in such measures that may thus result from early or late starting of contraceptive practice after the termination of pregnancy, the author proposes certain criteria for the inclusion of couples in studies of contraceptive effectiveness and for the length of time that couples should be observed.

Some implications of recent work in historical demography. John T. Krause. *Comparative Studies in Society and History* **1,** 2 (January 1959), 164-188.

According to a view that has had considerable acceptance, the demographic history of the industrial West involved a transition from high to low birth and death rates in which a lag in the decline of fertility behind that of mortality produced substantial growth. Whether a similar pattern can now occur in the pre-industrial areas of the present is a question of wide interest.

On the basis of a review of recent studies of Western demographic history, the author finds cause for doubt that the pattern just described was ever characteristic even of the West. He suggests that population growth rates in the pre-industrial period were highly variable and that this variability was due chiefly to fertility rather than mortality. The fertility variations, in turn, may be attributed to changes in nuptiality and to much more extensive and earlier use of birth control than has commonly been presumed. Hence the fertility decline after 1870 may be in part a return to earlier customs.

A corollary of pre-industrial population balance at moderate rates of fertility and mortality would be an age distribution stronger in the economically active age groups than is the case for the underdeveloped countries of the present. The author points out that if this interpretation of the past should be substantiated it would imply that "West Europeans on the eve of industrialization were in a much more favorable position than are most under developed countries today."

Notes on immigration statistics of the United States. E. P. Hutchinson. *Journal of the American Statistical Association* **53,** 284 (December 1958), 963-1025.

Official United States immigration statistics are a series notable for length, having begun in 1819, but not for perfection. This article meticulously sets forth the sources in which the data are to be found and the varying definitions and registration practices used by the successive agencies responsible for collecting the statistics. It furnishes both general comments on the main blocks of data and specific notes by single years for the period 1820-1910. The author concludes that it would be possible to improve the series by corrections based on available information but that major weaknesses would still remain.

It seems clear that in the future anyone who needs to use these statistics will wish to begin his study with this article.

Toward a conceptualization of demography. George A. Hillary, Jr. *Social Forces* **37,** 1 (October 1958), 45-51.

Whether, or in what sense, demography is an independent field of study is a question that demographers occasionally think about, though for the

most part it does not seem to be one of their major concerns. The present paper attempts to clarify the situation as it involves the relationship between demography and sociology. A survey of some of the definitions of demography proposed over the last hundred years suggests a tendency to narrow the field toward quantitative study of population size, composition, and change. To test whether what demographers actually do corresponds to what is implied in the definitions, an examination was made of the contents of eleven (highly assorted) major publications in demography and of a portion of the literature listed in a five-year run of *Population Index*. The author concludes that "agreement is extensive: the major emphases for almost all authors, as for the *Index* topics, remain demographic processes and composition" (p. 48).

The second half of the paper discusses the relation between demography and sociology at what the author calls the "field," "conceptual," and "special" levels of generality. It is concluded that the two areas cannot be separated, nor can they be equated, since one is concerned with man's quantity and the other with his social aspect.

On the whole, the article seems to the reviewer to be nearer the beginning than the end of a satisfactory conceptualization of demography. Though the content analysis of publications, as carried out here, is a fairly crude device for describing demography, it will be of passing interest to some readers for the comparison it gives among the works examined.

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